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BILATERAL TOTAL ADRENALECTOMY IN DIABETICS WITH DEGENERATIVE VASCULAR DISEASE

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It has been known for many years that diabetics have a tendency to develop premature arteriosclerosis However, during the past few years, there has come a realization that many young diabetics develop severe arteriolar degenerative disease in relation to the duration of the diabetes and to its previous clinical characteristics Roughly, the longer the duration of diabetes, and particularly the more severe and "brittle," the earlier will the vascular disease develop The earliest manifestation of diabetic vascular degeneration may be recognized in the form of micro-aneurysms in the retinal arterioles Later the manifestations of generalized vascular degeneration become widespread. Frequently the kidney becomes the greatest area of clinical pathology One stage of this renal vascular deterioration was defined by Kimmelstiel and Wilson,[1] when they described "intercapillary glomerulosclerosis" Proceeding beyond this nephrotic syndrome, the advanced stage of renal deterioration is characterized by marked hypertension, vascular accidents, nitrogen retention, marked proteinuria, hypercholesteremia, eventual renal failure and death Vascular changes in the retinal vessels produce clinical blindness as the disease unfolds

Among diabeticians, there has been much discussion concerning the cause of this degenerative disease Those individuals who believe in "free-control" have stated that this type of diabetic treatment has no specific effect on arteriolar degeneration Those who believe in physiological control of diabetes have claimed that this type of treatment may postpone degenerative vascular disease indefinitely This point remains unsettled

We have referred in previous publications[2, 3] to evidence that altered adrenal cortical function resulting from the complicated course of diabetics may well be responsible for arteriolar degeneration To summarize this evidence briefly, we may conclude that insulin hypoglycemia, either relative or absolute, is a profound stimulant of adrenal cortical secretion[4-7] Other evidence has been pre-

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Research paper 1164, Journal series, University of Arkansas

Read at annual meeting, South Central Section of American Urological Association, Colorado Springs, Colo October 18–20, 1954

[1] Kimmelstiel, P and Wilson, C Intercapillary lesions in the glomeruli of the kidney Am J Path, 12: 83, 1936

[2] Wortham, J T and Headstream, J W The effects of bilateral, total adrenalectomy in diabetics with advanced vascular disease In Third Annual Report on Stress, 1953, by H Selye and A Horava Acta, Montreal, 1953, p 195–202

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[4] Somogyi, M Insulin resistance produced by insulin hypoglycemia Fed Proc, 11: 289–290, 1952

[5] Gellhorn, E and Safford H Influence of repeated anoxia, electroshock and insulin hypoglycemia on reactivity of sympathetico adrenal systems Proc Soc Exp Biol Med, 68: 74–79, 1948

[6] [illegible] mphatic tissue in rats following injection of insulin Am J
F

[7] [illegible] nature of the protein catabolic response to adrenal cortical
e [illegible] hypoglycemia Endocrinol, 45: 170–177, 1949

sented that high blood sugars, particularly rapidly rising blood sugars, are also stimulatory to the adrenal cortex.[8-11] It is a logical assumption that when the blood sugar fluctuates widely, the adrenal cortical secretory functions are also widely fluctuant. Arteriolar degenerative phenomena have been produced repeatedly in experimental animals simply by the administration of excessive amounts of adrenal hormones which would be expected to fluctuate under such a situation.[12-15] More recently, a lesion which is identical to diabetic retinopathy has been produced simply by the administration of excessive amounts of cortisone.[16] Cortisone, of course, is the type of adrenal cortical hormone which would be expected to fluctuate widely in response to fluctuations in the blood sugar. In these days of various types of long-acting insulin, most diabetics experience wide fluctuations in blood sugar.

We have felt that diabetics with vascular disease might well benefit by stabilization of their adrenal cortical functions. Since this is impossible by medical methods, bilateral total adrenalectomy followed by constant maintenance doses of the vital adrenal cortical steroids was attempted. We were much encouraged in this project by the report of Green, Nelson and Dodds.[17] These authors reported favorable results upon the vascular lesions and upon the diabetes of a patient with malignant hypertension and diabetes following radical subtotal adrenalectomy. Further encouragement was given by the report of Poulsen[18] of marked improvement in the retinopathy of a young diabetic woman after the development of hypopituitarism due to postpartum pituitary necrosis (Sheenan's syndrome).

METHOD OF HANDLING

Seven patients have been studied before and after bilateral adrenalectomy. No surgical mortality has been experienced despite the precarious nature of the patients' vascular systems. After baseline studies and gross regulation of the diabetes, all patients were prepared with 300 mg. of cortisone acetate for 3 days prior to surgery, and no difficulty with vascular collapse or shock during the operative or postoperative period has occurred.

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[8] Freeman, H. and Elmadjian, F. L.: The relationship between blood sugar and lymphocyte levels in normal and psychotic patients. Psychos. Med., **9:** 226–232, 1947.

[9] Marks, P. A., Marks, D. T. and Jailer, J. W.: Depression of lymphocyte count after orally administered glucose. J. Clin. Endocrinol., **8:** 621, 1948.

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[11] Elmadjian, F., Freeman, H. and Pincus, G.: The adrenal cortex and the lymphocytopenia due to glucose administration. Endocrinol., **39:** 293–299, 1946.

[12] Selye, H.: Stress. The physiology pathology of exposure to systemic stress. Acta Inc., Publ. Montreal, 1950.

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[15] Selye, H. and Horava, A.: Third annual report on stress. Acta Inc., Publ. Montreal, 1953.

[16] Becker, B.: Diabetic retinopathy. Ann. Int. Med., **37:** 273–289, 1952.

[17] Green, D. M., Nelson, J. N. and Dodds, G. A.: Effects of adrenal resection on hypertension and diabetes. Fed. Proc. **8:** 60, 1949.

[18] Poulsen, J. E.: Recovery from retinopathy in a case of diabetes with Simmonds' disease. Diabetes, **2:** 7–12, 1953.

The posterolateral approach with the patient in the lateral position commonly employed in kidney surgery gives much the best exposure. The twelfth rib is resected and the incision is made through the rib bed. The wound is closed, the patient turned in the same position on the opposite side, redraped and the other adrenal is removed. *Braided wire sutures are used for closure by placing through-and-through sutures with exception of the skin while the patient is on the kidney elevator and then tied when the elevator is flattened.*

After surgery the cortisone dose is gradually reduced. The final maintenance dose was that which maintained the serum sodium, potassium, and chlorides within normal limits, the eosinophile count below 200 cells per cubic millimeter, and the patient free of symptoms of adrenal insufficiency. This dose is generally in the range from 25 mg. to 50 mg. daily.

CLINICAL MATERIAL

The clinical course of each of the patients to the present time will be presented.

Case 1. L. C. was a white, married woman aged 23 years, para 8-7-1. Her diabetes had been very "brittle" and labile during most of its 13 years' duration, and she had experienced diabetic coma 7 times. Four years before admission to our service, she had experienced severe hypertension and proteinuria during a pregnancy. For over 3 years hypertension, chronic edema, and poor diabetic control had been constantly symptomatic. Progressive and rapid visual loss had been noted for 1 year.

The preoperative blood pressure averaged 160/120. Fourteen months after adrenalectomy it averaged 107/80. The average preoperative value for serum nonprotein nitrogen was 55 mg. per cent, and it now averages 48 mg. per cent. Urinary protein has fallen from an average of 5.5 gm. per 24 hours to .75 gm per

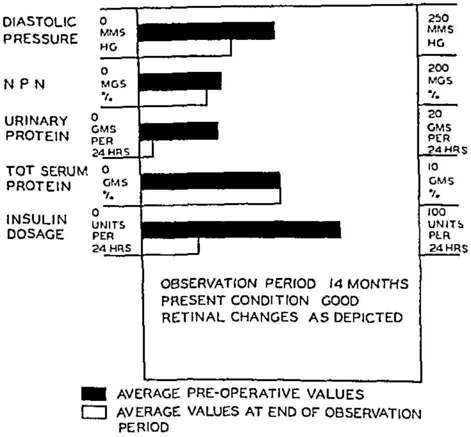

FIG. 1

24 hours. Close diabetic control was impossible preoperatively, but crude control was obtained with 70 units of insulin daily. Control is now maintained with 20 units of insulin daily. These changes are depicted graphically in figure 1. Chronic generalized edema has disappeared and there has been remarkable improvement in visual acuity. Changes in one optic fundus during the first 4 months after adrenalectomy are shown in figure 2. There has been little change in this fundus during the 10 months which have intervened since the last sketch. The patient has regained a remarkable sense of well-being.

Case 2. G. H. was a white man, aged 54 years. A diagnosis of diabetes had been made 22 years before admission but after a few months of diet therapy glycosuria had disappeared. From that time until admission, no diabetic precautions or observations had been taken. The presenting complaints were those of severe, intractable headaches and of rapid visual loss.

The average preoperative blood pressure was 180/93. Thirteen months after surgery the blood pressure averaged 165/85. The average preoperative value for serum nonprotein nitrogen was 55 mg. per cent. During a routine hospital observation after adrenalectomy, a sharp rise in the nonprotein nitrogen was noted. This proved to be the first evidence of adrenal insufficiency, due to inadequate replacement therapy. Since correction there has been a progressive decrease in nitrogen retention, and the average nonprotein nitrogen is now 74 mg. per cent. The urinary protein has fallen from a preoperative average of 6.5 gm. per 24 hours to 4.0 gm. per 24 hours. The patient had never been regulated upon insulin preoperatively and diet control was not satisfactory. Insulin was used during the acute, operative stress period, and now the blood sugar control is adequate with diet therapy alone. There has been no further progression in his severe diabetic retinopathy. Retinal hemorrhages have ceased, retinal edema has decreased, and the visual acuity is moderately improved. The patient has an astonishing sense of well-being and almost all symptoms have disappeared.

Case 3. B. R. was a white, married woman aged 40 years, gravida 4-1-3.

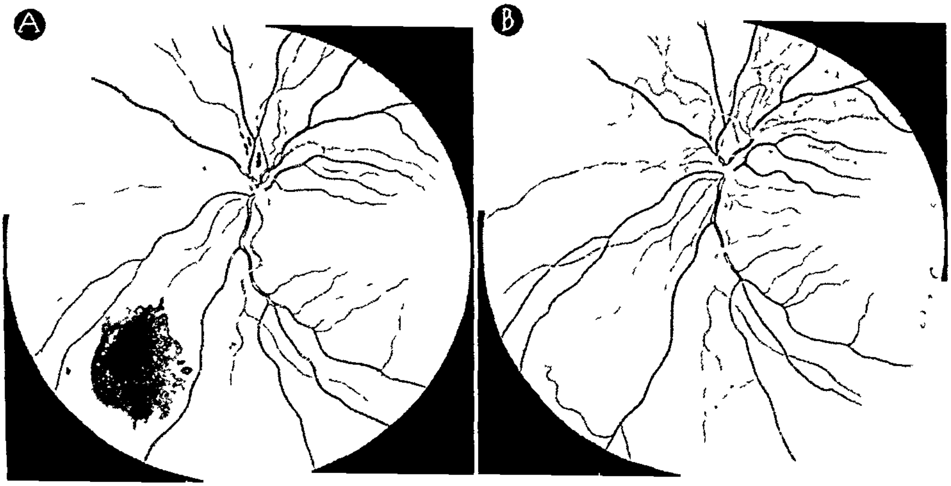

FIG. 2. *A*, drawing of eye ground before adrenalectomy. *B*, 4 months after adrenalectomy.

Her entire 8 years of diabetes had been difficult ones, and she had never been closely regulated Several episodes of diabetic coma and innumerable severe insulin reactions had been experienced On admission she was in a state of hypertensive encephalopathy complicated by mild diabetic acidosis

The average preoperative blood pressure was 200/100 Four and one-half months after surgery, before death, the average blood pressure was 190/115 The serum nonprotein nitrogen rose progressively from a preoperative average of 65 mg per cent to a predeath average of 120 mg per cent Only a slight decrease in urinary protein occurred, and there was no rise in her subnormal total serum proteins The insulin requirements fell from 40 units to 30 units daily and the degree of diabetic control was much improved Despite largely unfavorable results, there was visual improvement based upon cessation of retinal hemorrhages and resorption of retinal edema Generalized edema had been intractable before adrenalectomy but became readily controllable after surgery She died of a cerebral vascular accident during a course marked by progressive renal failure

Case 4 M T was a white, married woman, aged 21 years, para 0 Five episodes of diabetic coma, innumerable severe insulin reactions and gross neglect had characterized her 14 years of diabetes Fifteen months before admission to the University service both optic globes had been removed due to intractable pain from secondary glaucoma Irremediable edema had been present for 1 year, and she was admitted in a state of hypertensive encephalopathy

The average preoperative blood pressure was 220/140 Eight months after adrenalectomy, at the last observation before death, her blood pressure was 210/140 The average serum value for nonprotein nitrogen fell from 51 mg per cent before surgery, to 45 mg per cent The urinary protein fell from a preoperative average of 5 2 gm per 24 hours to 2 7 gm per 24 hours before death The insulin requirement fell from 60 units daily before surgery, to 35 units daily before death The patient became edema free and encephalopathic symptoms disappeared There was an amazing improvement in well-being She remained active and asymptomatic, with her diabetes under good control, until shortly before death She died of adrenal insufficiency after leaving the care of the University service

Case 5 E W was a white man, aged 27 years After several years of good diabetic control, his adolescent and adult years were characterized by very poor control Total duration of his diabetes was 18 years Onset of rapid visual loss occurred 2 years before admission Bilateral severe retinal detachment and retinitis proliferans were present on admission

The average preoperative blood pressure was 166/108 The months after adrenalectomy it averaged 150/102 The average preoperative value for serum nonprotein nitrogen was 42 8 mg per cent, and it now averages 56 5 mg per cent

Urinary protein has risen from an average preoperative value of 6 56 gm per 24 hours to a present average of 8 31 gm per 24 hours Initial diabetic control was achieved with an average of 67 units of insulin daily The diabetes is now well controlled with 45 units of insulin daily There has been no change in the retinal disease

Case 6. M. G. was a white, married woman, aged 56 years, para 0. Diabetic symptoms had been present for several years but the diagnosis had been made only 3 years before admission. Chronic edema, severe headaches and rapid visual loss had been noted for 1 year. Retinal examination revealed advanced arteriolosclerosis, innumerable small retinal hemorrhages, retinal edema and moderate exudation.

The average preoperative blood pressure was 160/95. Ten months after adrenalectomy, it averaged 107/73. The average preoperative value for serum nonprotein nitrogen was 39.5 mg. per cent, and it now averages 34 mg. per cent. Preoperative urinary protein averaged .71 gm. per 24 hours, and has now fallen below measurable quantities. Good diabetic control was established with 20 units of insulin daily before surgery. No insulin is now required for close control. There has been cessation of retinal hemorrhages and clearance of retinal edema, with significant improvement in visual acuity.

Case 7. R. T. was a white man, aged 29 years. Diabetes had been present 24 years and the patient had ignored all precepts of good diabetic care. Myocardial infarction had occurred at 27 years of age. Chronic edema had been present for 1 year, and he had been clinically blind for 1 year due to severe diabetic retinopathy.

The average preoperative blood pressure was 197/125. Before death it averaged 185/125. The average preoperative value for serum nonprotein nitrogen was 69.3 mg. per cent. Before death the value reached 170 mg. per cent. The preoperative average for urinary protein was 10.9 gm. per 24 hours, and before death it fell to 5.5 gm. per 24 hours. The total serum protein, however, fell sharply during this period. The insulin requirement fell from 55 units to an average of 31 units daily after surgery. There was no retinal improvement.

CLINICAL ANALYSIS

Some of our patients have done very well, and there has been evidence of minor reversals in the vascular disease process. Others have shown continued progression in their vascular disease, and they have died from it. Our series is too small to permit statistical analysis, but comparison of routine preoperative observations may yield some ideas as to which patients will benefit from adrenalectomy. (See figure 3.) We have averaged the preoperative observation values on the 2 patients who have responded best to the procedure (cases 1 and 6). We have also averaged the preoperative observation values on the 3 patients who showed little response to the procedure and who are now dead (cases 3, 4, and 7). From these comparative figures we gather that the preoperative level of diastolic blood pressure is of little prognostic value. The unsuccessful group had only slightly higher pressures than did the successful group. Perhaps the nonprotein nitrogen averages were more valuable. Those patients who did well had values for nonprotein nitrogen at the upper levels of normal, while the unsuccessful group of patients had significantly elevated nonprotein nitrogen levels. The total urinary protein values were even more distinctive. Our successful patients had average

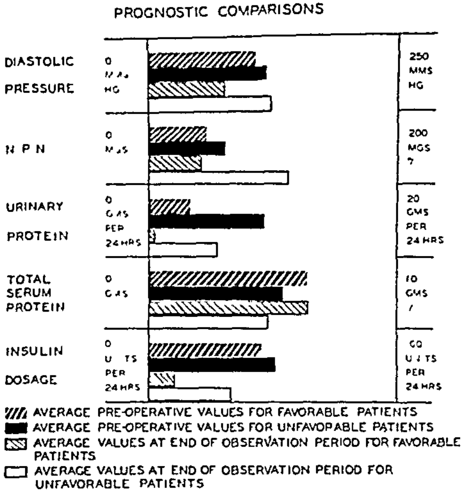

FIG 3

24-hour urinary protein values of less than 5 gm , but the unsuccessful group had average values of near 10 gm per day The age of onset of the diabetes held no prognostic significance, and we found little of value in analyzing the duration of the diabetes in the two groups of patients A sharp fall in insulin requirement is noted in the successful patient after adrenalectomy as well as the ability to maintain close control on this low dosage We can summarize by saying that no single clinical factor that we have observed is of excellent prognostic value It seems that our successful results have been inversely proportional to the degree of vascular pathology determined We no longer consider doing adrenalectomies when we have evidence of far advanced renal deterioration

SUMMARY

Bilateral adrenalectomy has been performed in a small series of diabetics with degenerative vascular disease

The results lend evidence to the attitude that vascular deterioration of the general types seen in diabetics may involve abnormal adrenal cortical function "Brittleness" and increasing insulin requirements point to such a functional disturbance of these glands

A summarization of the case reports has been presented as well as some opinions as to the prognostic significance of the findings

It appears that if adrenalectomy is to be successful it should be done fairly early in the arteriolar degenerative processes and the results suggest that in well-selected patients it is a relatively practical and hopeful therapy

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NEPHROCALCINOSIS IN ROUTINE NECROPSIES; ITS RELATIONSHIP TO STONE FORMATION

HUGH A. STOUT, ROBERT H. AKIN AND EUGENE MORTON

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Metastatic calcification is defined as the translocation of calcium from the skeleton to the soft tissues, particularly to the kidney. This condition is quite well known to experimentalists, especially in cases of hyperparathyroidism. Albright and Reifenstein[1] found nephrocalcinosis or gross renal stone formation in 81 per cent of 64 cases of hyperparathyroidism.

The same metastatic calcification with a high incidence of stone formation is well known to occur in other conditions which cause a great deal of bone destruction or osteoporosis from trauma, prolonged immobilization[2] and osteomyelitis. It occurs also in marked alkalosis as in protracted vomiting, excessive ingestion of alkali,[3] and in vitamin D poisoning.[4]

This deposit of metastatic calcium occurs in organs which excrete acid, the lungs excreting carbonic acid; the stomach, hydrochloric acid; and the kidneys, sulfuric, phosphoric, and organic. Surely the calcium must combine with the weak acid to produce a salt when calcium is present in excess and particularly when the cell is sick or dying and the acid cannot be excreted before the calcium is forced upon it.

Now nephrocalcinosis is a term that has been loosely applied to miliary calcifications in the kidney whether these be metastatic, metabolic, toxic, infectious, local, systemic, vascular, lower nephron, hyperexcretory, few or many. The term therefore has very little clinical meaning unless an etiological prefix is attached. We would therefore propose that two words be used when possible, such as metastatic nephrocalcinosis.

Vermooten[5] discussed the significance of microscopic calcifications in the papillae of the kidney and suggested that these might ulcerate into the pelvis to form a nidus for stone formation. Anderson and McDonald,[6] Henle,[7] Beer,[8] and Huggins[9] have studied the incidence of calcinosis in routine necropsies and in microscopic calcification or gross stone formation.

Lower nephron nephrosis must be considered here because we propose to show microphotographs from cases of proved lower nephron nephrosis in which there is extensive metastatic nephrocalcinosis. Lower nephron nephrosis is best under-

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Read at annual meeting, South Central Section of American Urological Association, Colorado Springs, Colo. October 18–20, 1954.

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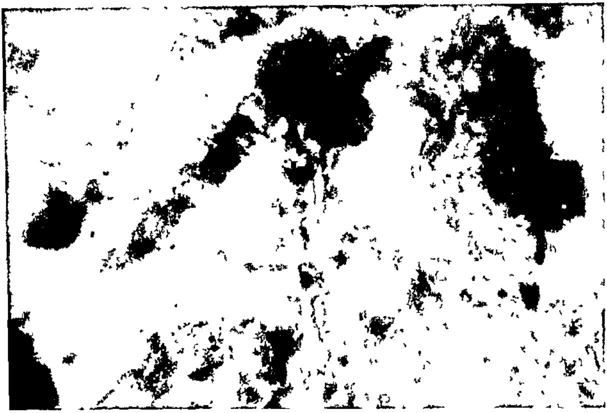

Fig. 1

stood from the picture described so often in World War II by Mallory[10] and others and it develops in the following manner. Suppose a man suffers a severe hemorrhage and shock, then to compensate for this a generalized constriction of the peripheral arteries occurs for the purpose of holding the remaining blood in the vital organs, that is, the heart, lungs, and brain. In order to hold the blood in the vital motor organs, then the peripheral arteries in the kidneys which supply the lower nephrons also constrict and result in anoxemia of the lower nephrons within a very short period of time. Portions of the lower nephron epithelium slough out in patchy manner leaving defects or holes in the lower nephron through which concentrated excretory poison can be reabsorbed into the circulation and with resultant anuria and uremia even after normal filtration pressure through the glomeruli has been established. Concentrated poisons as well as shock contribute to lower nephron degeneration and necrosis and the list of poisons capable of this is now a very long one.

Under these conditions it would not be unusual for the subadjacent interstitial tissue to become toxic and subject to calcification by the concentrated calcium salts leaking through these defects. That nephrocalcinosis may begin in the interstitial and basement membrane tissue seems quite likely from the experimental work on animals.[11]

Randall[12] in a long and detailed paper published in 1940 found calcific plaques in and on the papillae of the kidney in 19.6 per cent of 1154 routine autopsies. His photographs show nephrocalcinosis in the lower nephron regions above the plaques, but his attention was focused primarily on the plaques as niduses for stone formation. We do not wish to detract from the importance of this dis-

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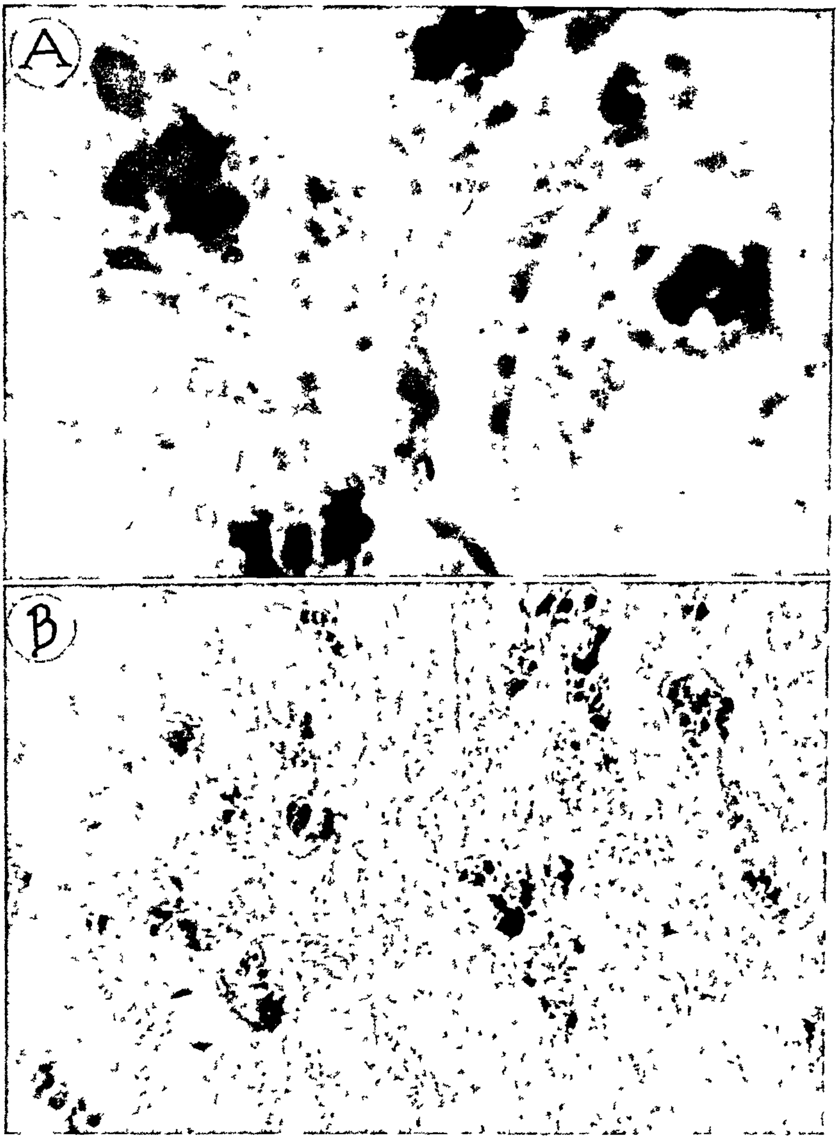

FIG 2

covery of these plaques, but in the light of our present findings and knowledge we believe that a more logical explanation can be given for their origin. He believed that certain bacterial toxins and local pathological processes in the papillae were primarily responsible for these calcifications. This viewpoint makes it difficult to explain the innumerable cases of severe bacterial infection and pyelonephritis in which no such calcifications occur.

Our own interest in this problem was especially aroused by a necropsy examination which we performed on a young man 31 years of age who lay in bed for 1 month with a fever of unknown origin and clinically was thought to represent a case of acute disseminated lupus erythematosus or possibly polyarteritis nodosa. He was given rather large amounts of intravenous ACTH during his tubular tissue. The lesion in the lower nephron region involves primarily the collecting tubules with extension frequently into the interstitial tissue.

To show the distribution of these lesions we are reproducing microphotographs from five of our routine necropsies in which there were innumerable areas of calcification and we are presenting their case histories to be contrasted with the case histories of five representative cases in which not any microscopic calcifications were found.

CASES WITH INNUMERABLE CALCIFICATIONS

Case 1. This type of case is well known to produce metastatic calcification but we present it primarily to show the distribution of the lesion in a patchy manner in the region of the lower nephron which happens to involve the ends of renal

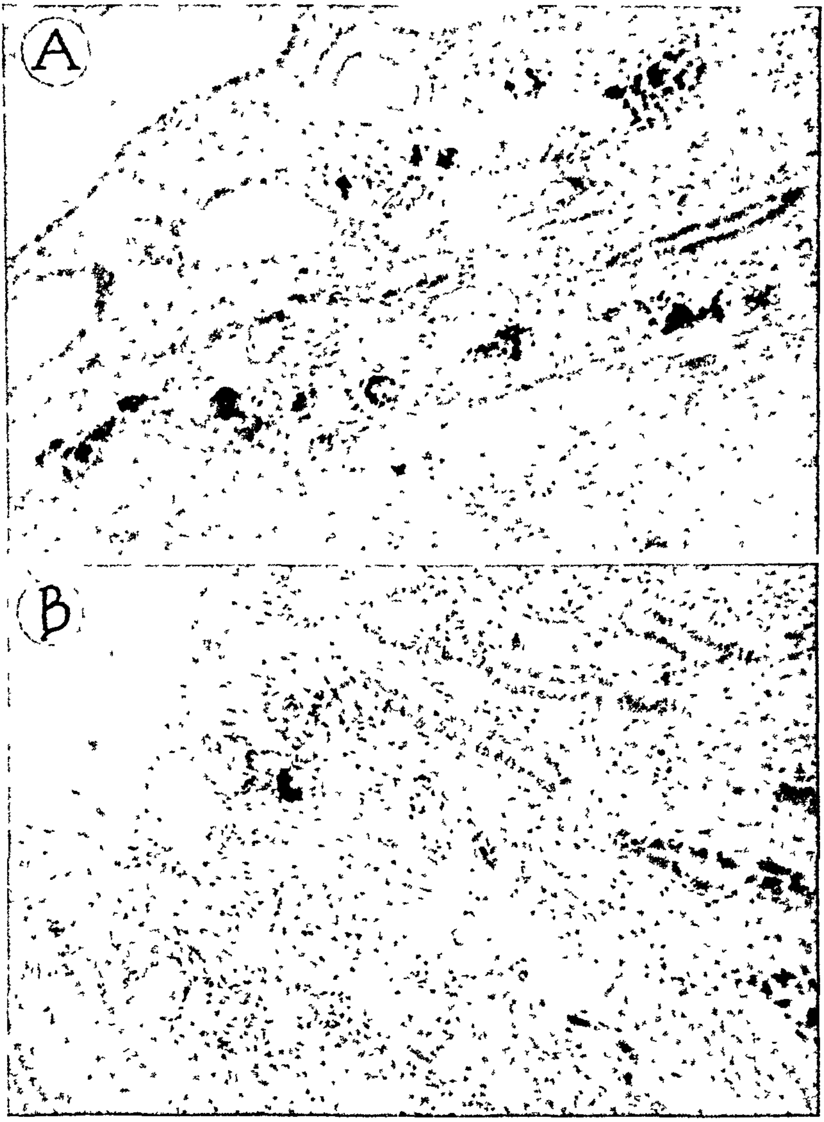

FIG. 3

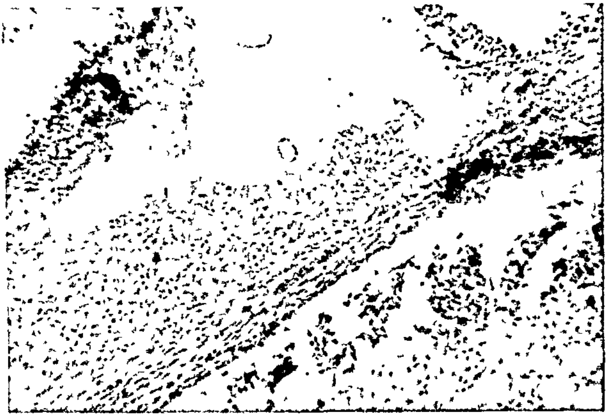

FIG. 4

papillae. The patient was a 60-year-old white woman who had bilateral carcinoma of the breast, the second breast having been radically removed approximately 2 years before death. She had metastatic lesions to the vertebrae as well as to the lungs and lay in bed for months prior to death requiring narcotics in addition to testosterone (figs. 3 and 4).

Case 2. A white man, aged 58 years, A-83-'53, had complete obstructive jaundice for 2½ months or more. An exploratory surgical operation was performed 2 months prior to death and a carcinoma of the ampulla of Vater was suspected. His jaundice continued to deepen in spite of surgery, however, and he died with the so-called hepatorenal syndrome. Autopsy examination showed extensive carcinoma in the head of the pancreas surrounding the major bile ducts with metastases to the liver. Microscopic examination of the kidneys showed advanced cholemic nephrosis with bile casts in the collecting tubules and areas of calcification in lower nephron area in all sections of both kidneys (fig. 5, *A*). In figure 5, *B* one sees calcifying tubular epithelium.

Case 3. A white man, aged 71 years, A-23-'53, had an exploratory operation 10 years prior to death for severe hematuria, no tissue removed. Two years later a left nephrectomy was done for squamous cell carcinoma of the renal pelvis. X-ray therapy followed. Approximately 2 years before death an 8 pound tumor involving the left ureter was removed. After this the patient lost a great deal of weight. At autopsy examination metastatic squamous cell carcinoma to the liver and lungs was found, but the right kidney appeared normal except for hypertrophy to 225 gm. Figure 6 shows numerous areas of calcification involving tubules. They are even more numerous in the pyramids, but this picture shows that they can often be found also in the parenchyma. The glomeruli are not involved.

Case 4. A white man, aged 60 years, A-42-'53, was admitted after vomiting

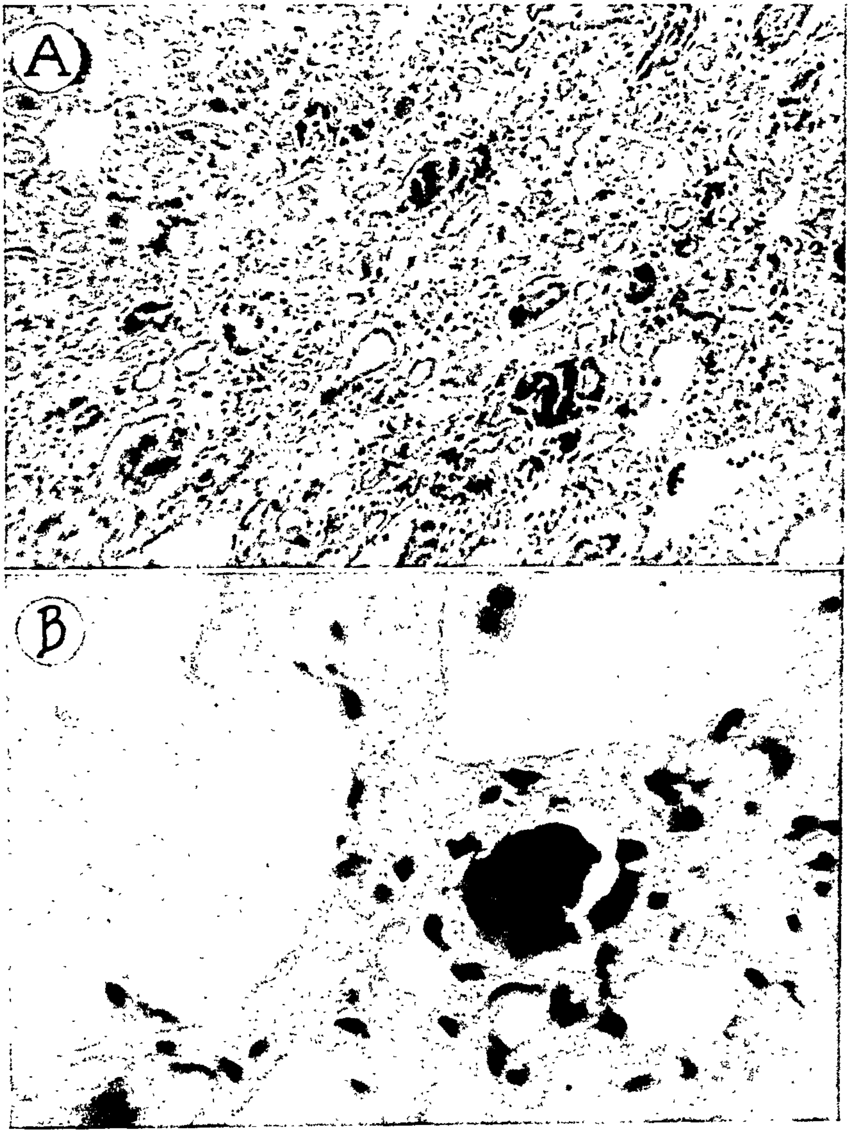

FIG. 5

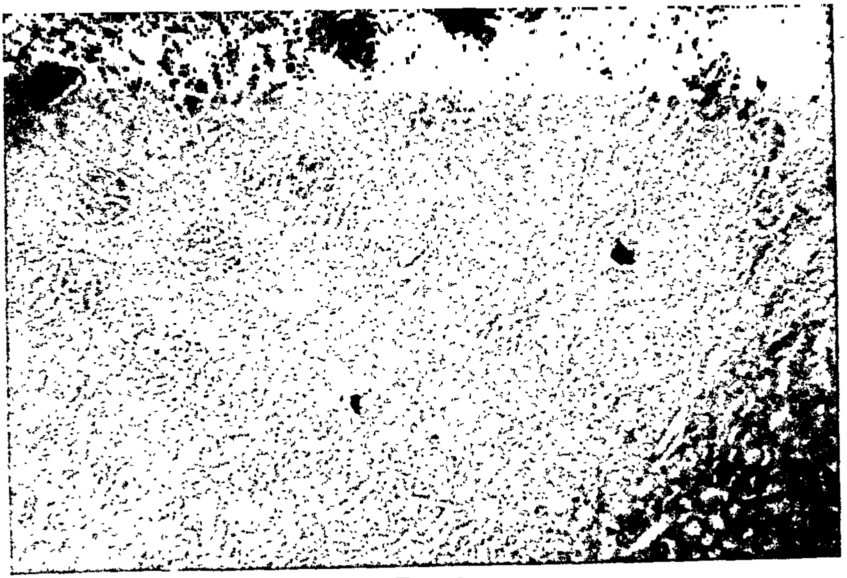

FIG. 6

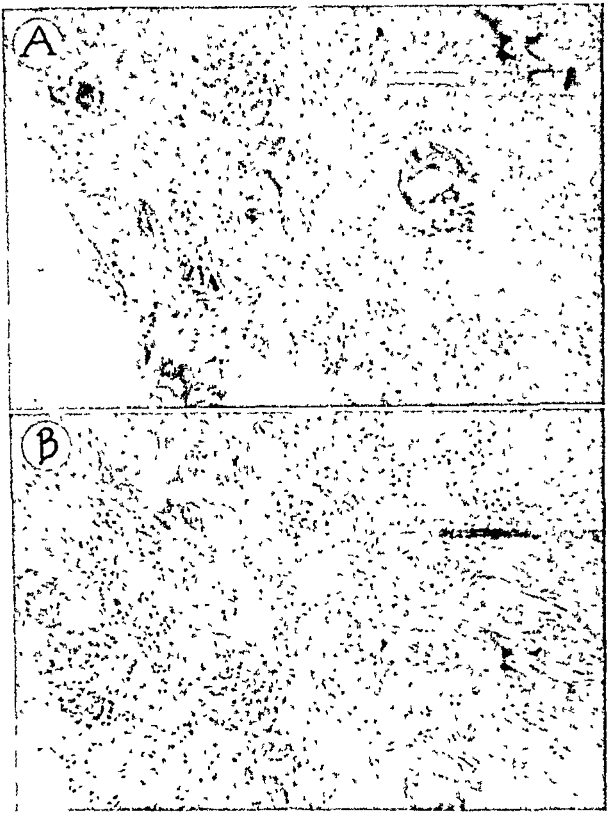

FIG. 7

for 7 days. He had been treated for peptic ulcer for 8 days. The patient was in shock and was prepared for surgery. A gastro-enterostomy was performed and death occurred from pulmonary embolus 9 days after surgery. He died 27 days after admission. Autopsy showed grade 3 atherosclerosis and arteriolosclerosis; the heart weighed 435 gm. Figure 7, *A* shows calcifications involving lower tubules and early plaque pathogenesis on the papillae of the kidneys. Figures 7, *B*, 8 and 9, *A* show a caseous, necrotic and dead colloid paste entering gross lesions. The original microscopic calcification is in a degenerating cell or nest of cells. The pathogenesis of "plaques" on the pelvis is shown along with calcification of lower nephron lesions.

Case 5. A white woman, aged 83 years, A-36-'53, had been in congestive heart failure for at least 6 months with hypertension requiring digitalization. She had

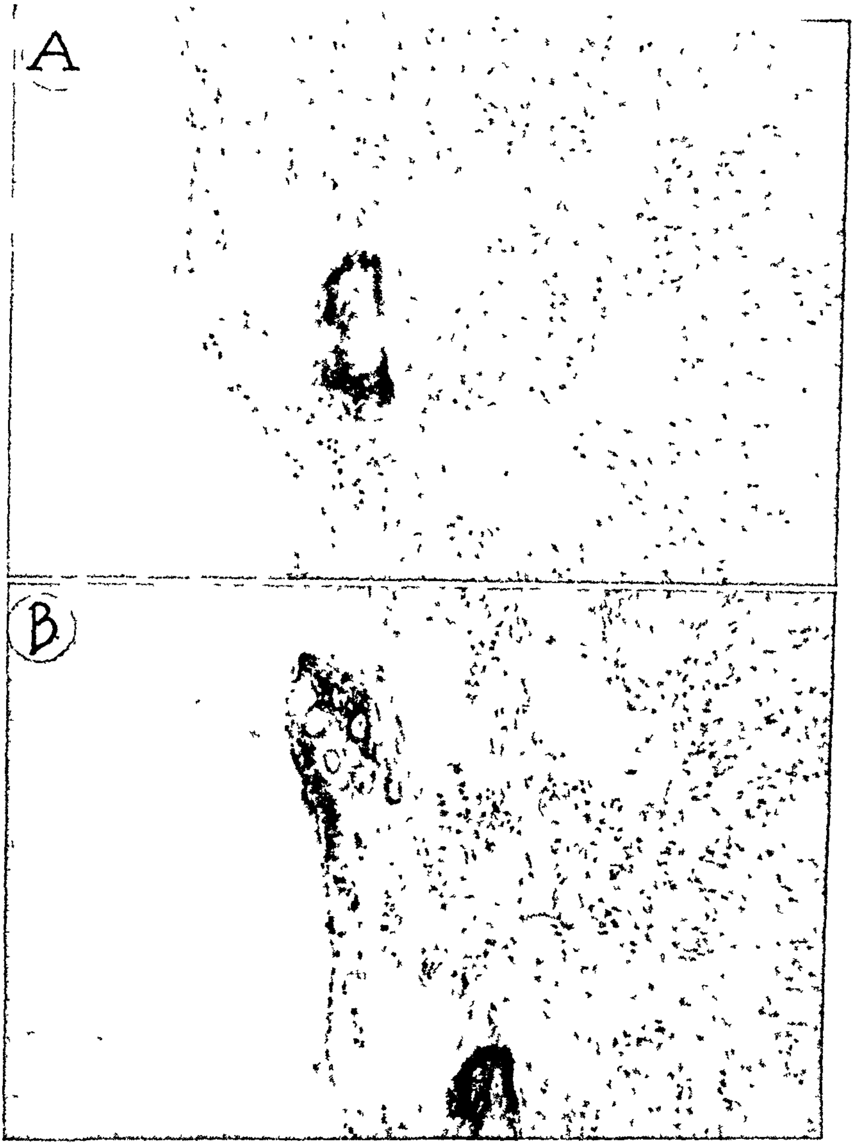

FIG. 8

lost considerable weight because of not eating and vomited persistently for one week prior to admission. Urinalysis in the hospital was negative. Death occurred on the twelfth hospital day. Autopsy examination showed a grade 4 atherosclerosis with marked arteriolosclerosis in the kidney. The heart weighed 500 gm. Her course at the hospital showed her in shock during the last few days. There was volvulus of the ileum in the center of which was a Meckel's diverticulum which showed ischemic necrosis. Figure 9, *B* showed nephrocalcinosis with several small areas of early plaque formation on the ends of papillae.

CASES IN WHICH THERE WERE NOT ANY CALCIFICATION

Case 1. A Negro, aged 46 years, A-11-'54, was previously well but nausea and vomiting developed the day before admission. He rapidly became comatose:

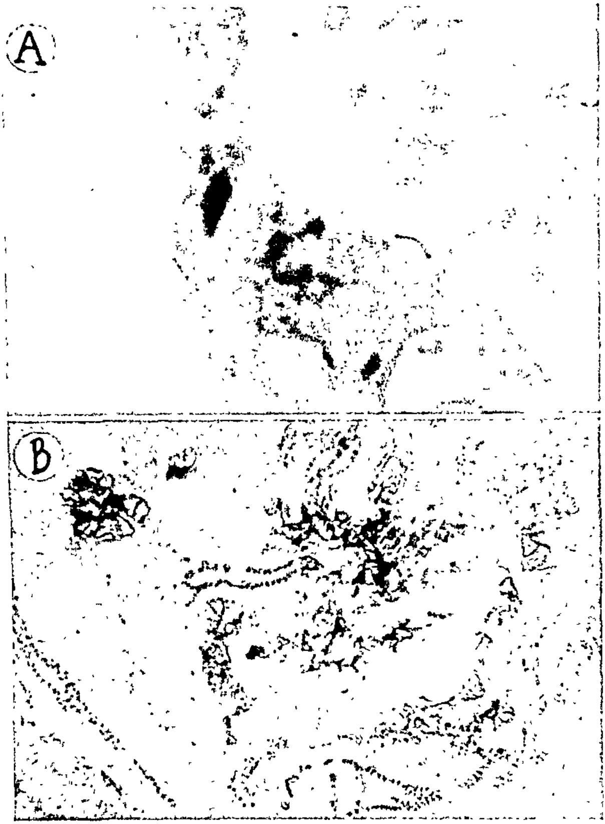

FIG. 9

blood pressure 50/0, respiration 36. Physical examination was otherwise essentially negative. The fasting blood sugar was 986 mg. per cent, CO_2 13 volumes per cent, acetone 4+. He was given fluids and 550 units of insulin in 50 to 100 unit doses but died 15 hours after admission without regaining consciousness. Autopsy examination showed essentially normal kidneys with no areas of calcification.

Case 2. A white man, aged 53 years, A-51-'54, had been previously well except for being a heavy drinker of alcohol. He was found unconscious in his grocery store late in the afternoon of the year's hottest day, 107F on the outside. His body temperature on admission to the hospital was 108F axillary, which gradually dropped to 105F. His estimated body temperature was 110F. The autopsy examination showed the typical neuronolysis with large nerve cells disappearing and leaving only blank spaces, characteristic of severe heat stroke and high body temperature. The necropsy otherwise showed essentially normal heart and arteries and normal kidneys with no evidence whatever of nephrocalcinosis. The patient died 4½ hours after admission to the hospital.

Case 3. A white woman, aged 79 years, A-3-'54, had been previously well although she was known to have moderate hypertension (220/100). She suffered sudden, severe, substernal pain the night before admission. She did well for 3 days in the hospital. The blood pressure remained at about 180/100. She died suddenly on the fourth hospital day. Autopsy examination showed fresh coronary thrombosis with marked atherosclerosis but extremely little calcification in the coronary arteries. The smaller arteries of the kidneys were essentially normal for this age. The heart weighed 560 gm. The kidneys microscopically appeared essentially normal for this age, showing no evidence of nephrocalcinosis.

Case 4. A white man, aged 73 years, A-2-'53, had been previously well but was found unconscious in his house after having been seen entering the house 3 days previously, although the neighbors had noticed smoke coming from the chimney. On admission his temperature was 96F. One pupil was smaller than the other, respirations were 36 per minute. The blood sugar showed 520 mg. per cent, CO_2 25 volumes per cent. Intravenous fluids and insulin were given but the patient died in 12 hours. Autopsy examination showed a fresh myocardial infarction. The heart weighed 378 gm. The kidneys appeared essentially normal for this age, showing no evidence of microscopic calcification.

Case 5. A white man, aged 72 years, A-6-'54, underwent suprapubic prostatectomy for adenocarcinoma of prostate 1 year prior to admission. One week prior to admission he had nausea, vomiting, and pedal edema. The blood pressure was 170/90. The nonprotein nitrogen was 88 mg. per cent to 217 mg. per cent before death. Chest x-ray was negative. The patient did well in the hospital until 3 days before death when urine output ceased. The autopsy examination showed severe acute and chronic pyelonephritis bilaterally. Prostatic carcinoma was present about the neck of the bladder. There was no evidence of calcification in either kidney.

In figure 10 we show a drawing of the distribution of these areas of microscopic calcification in general. It will be noted that there is a patchy distribution identical to the lesions seen in lower nephron nephrosis, the concentration being greater the lower in the pyramid one seeks. Whether or not the tip end of the papillae is involved depends upon whether the patchy distribution happens to involve the end of the papillae. We believe that one pyramid may be involved to the exclusion of another because the blood supply is diminished in the affected pyramid longer than in the unaffected one.

It will be noted that in the cases of marked nephrocalcinosis there was repeated, severe, shock-producing disease whereas in those without nephrocalcinosis death occurred without evidence of previous or present disease likely to produce lower nephron destructive lesions. Our studies throughout this series show, as is already generally known, that chronic and acute pyelonephritis, abcesses and even infarcts of the kidney are not associated with calcification. We believe this is because the blood supply to those areas is impaired and calcium is neither filtered into nor concentrated in them.

Our cases which showed innumerable microscopic calcifications include cases of multiple myocardial infarction, severe hypertension with group 3 and 4 arteriosclerosis complicated by previous surgery, cerebral vascular occlusions, uremia, pneumonia and conditions producing not only shock but severe toxemia and often vomiting and dehydration. The other conditions were mitral stenosis complicated by congestive failure and cerebral vascular occlusion, multiple myeloma, multiple hemiplegias, complicated by pneumonia, with unusually high temperature, acute, severe peritonitis in older people, and hip fracture followed by heart failure and shock.

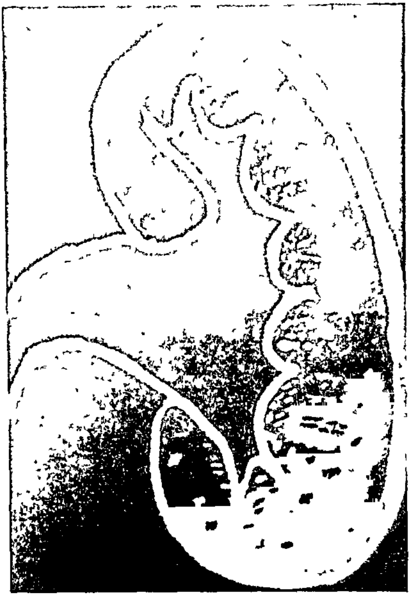

Fig. 10

In those cases which did not show nephrocalcinosis there were, of course, the newborns and children, diabetic acidoses, sudden deaths with no previous severe illnesses, and several cases of carcinoma without metastases to bone. In other words, these were not febrile, relatively nontoxic, and not in shock. For example, one white man, aged 58 years, had palliative removal of carcinoma of the rectum 2½ months before death with colostomy, followed by ascites, and died of gastrointestinal hemorrhage. Another white woman, aged 74 years, had had 10 inches of intestine removed 20 years prior to death for obstruction, and was operated on again 1 year after that for adhesions. She had hypertension for several years and entered the hospital for low abdominal pain. She was promptly explored surgically but died 2 days later, the brain at necropsy showing a fresh cerebral infarct. Her heart showed a healed myocardial infarct. She was well cared for promptly and with each illness, all of which may well have protected her kidneys from lower nephron damage. Another case, a white woman, aged 44 years, had cirrhosis of the liver and a cholecystectomy for gallstones 5 months prior to death. She did well but 2 weeks prior to admission hemiplegia developed and the patient died 37 hours after admission to the hospital. Autopsy showed a huge cerebral infarct with liver cirrhosis and wet lungs following intravenous fluid. The kidneys including their arteries and arterioles appeared normal.

We have limited our clinical study in those cases without nephrocalcinosis to those fifteen in the year 1954, because we cut far more sections and had both whole kidneys to section in every case. Every pyramid was sectioned one or more times and we feel far more certain of the absence or almost complete absence, anyway, of microscopic calcification. We realize that more cases need to be examined, but since the contrast is quite marked and clear-cut we feel this report is justified.

The average hospitalization days for those with no calcification was approximately 7.9 days per patient while the average hospital stay for those with innumerable calcifications was approximately 21.6 days, including in both instances days of past hospitalization. Actually, if we count days of immobilization in bed there was even more difference since in the cases of nephrocalcinosis there were multiple myeloma, mitral stenosis, previous cerebral vascular occlusions, previous myocardial infarctions, metastatic malignancies to bone, recurrent carcinoma, hip fracture, and conditions which would confine the patients to bed for months at a time. However, metastatic nephrocalcinosis can occur within a few days' time. One of our patients, a 60-year-old white woman, showed innumerable early lesions after 5 days of severe generalized peritonitis following ruptured appendix with no previous history of serious illness. For years experimentalists have been able to produce nephrocalcinosis in animals within 3 days after administering parathyroid hormones. We therefore believe that the lesions appear in showers during an illness which produces the set of conditions mentioned below.

DISCUSSION

Severe and persistent vomiting was present in the great majority of our cases of calcinosis sufficient to lead to dehydration with probable alkalosis and peripheral vascular collapse in many. Others had prolonged immobilization with resultant osteoporosis, due in some instances to bone destroying lesions. Those outside these two categories had severe shock-producing disease long enough before death to cause lower nephron damage and immobilization plus increased output of their own ACTH; others had high temperature with severe toxemia and dehydration, and were given ACTH (2 cases), or cortisone, which is known to produce osteoporosis. There was even excessive administration of alkali and calcium in an ulcer patient who also had *prolonged gastro-intestinal hemorrhage*. Seventy-one per cent of our cases with nephrocalcinosis had marked arteriosclerosis and hypertension as compared with 11.8 per cent of those without it. The relationship seems to be that *shock and impaired blood flow through the kidney* are more easily produced in the hypertensive. The blood supply to the kidney is intact longer and returns to normal more quickly in the normotensive. This is probably the main reason why infants and children do not develop nephrocalcinosis. Anderson and McDonald[5] did not find it in patients under 9 years of age. This also makes it seem reasonable that degenerative or necrotizing lesions of the lower nephron precede the calcification, even when it is seen in the adjacent basement membrane.

We therefore believe that two basic conditions must coexist to produce nephrocalcinosis, namely, 1) *damage to the lower nephron* and 2) *increased calcium concentration actively flowing through the lesion*.

Such conditions are merely accentuated by dehydration and if alkalosis is necessary it can be produced by the increased calcium concentrated upon the autolytic organic acid radical made available at the particular locus of degeneration. These two conditions can only be met systemically or from above, and not ascendingly or locally from below. Toxins may damage the lower nephron both by producing shock and by concentrated excretion.

Most of our cases are not of the infectious type as shown by sterile urine cultures in some, and by the fact that broad spectrum antibiotics were given in most. Besides, the literature has already quite well shown that reasons other than infection exist for most if not all nephrocalcinosis.[1, 5, 6] In proved pyelitis, pyelonephritis, abscesses and renal infarcts, calcification is notoriously absent.

In all of our cases of marked nephrocalcinosis, therefore, we can find the aforementioned conditions met clinically. Since the same distribution is present in all of the early cases, and since clinical reasons can be found for those cases showing a few areas of calcification, for example, virus pneumonia or measles or dysentery with vomiting, immobilization and fever for a few days, then we would not consider it unusual for a large number of adults to show such lesions.

There is a caseous paste seen as the microscopic lesions grow in size which is similar to the necrotic center of the tubercle in tuberculosis. This, however, is a characteristic of the larger lesions and is in the gross lesion and the gross renal stone has similar dead colloid and organic material in it. Its growth is not true crystal growth known to physical chemists. The microscopic lesion begins in a degenerated cell and necrotic cellular material and as yet unclassified organic binding material remains a part of the growing process from then on. The only thing likely to break up such a stone, to date at least, is some type of surgical instrument.

In order to prevent microscopic stone formation, therefore, we recommend the following measures.

1) Treat and prevent shock producing disease in time to protect the kidney whether it be associated with surgical operations, trauma, chemical poisoning, toxemias associated with fever, cardiovascular disease or other

2) Treat or prevent vomiting, diarrhea, profuse sweating and excessive diuresis, particularly in bed-patients, to prevent not only alkalosis but increased concentration of calcium excreted.

3) Prevent prolonged immobilization, osteoporosis and bone destruction.

4) Avoid administration of calcium and alkali particularly in the bed-patient.

5) Dilute the blood in toxic states and administer weak acid such as lactic, acetic and HCL.

6) Keep the blood pressure up in hypertensives ill in bed.

7) Avoid ACTH and cortisone over long periods of time in bed-patients.

SUMMARY

We have presented a study of nephrocalcinosis in 147 routine necropsies.

Fifty-four per cent of our cases showed nephrocalcinosis.

A clinical correlation is presented to show systemic cause, along with microphotographs, which depict multiple lesions in the lower nephron with the patchy distribution of lower nephron nephrosis occasionally resulting in plaque formation on the papillae.

Evidence is presented to show that in those cases with numerous microscopic calcifications in the kidneys the condition is due to metastatic calcification in lower nephron lesions. The distribution of the lesions and clinical evidence are similar in most of the remaining cases and we assume that most if not all of the calcinoses are due to a similar condition of different degrees of severity.

The lesions apparently occur in showers and develop within five days' time or less.

The relationship to plaque and stone formation is discussed.

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MALIGNANT TUMORS OF THE RENAL PARENCHYMA IN ADULTS

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Most of us have found ourselves at one time or another operating on a kidney tumor that is grossly inoperable We may then be faced by the awesome predicament of being unable to obtain sufficient hemostasis to terminate the procedure only by going ahead and removing the kidney, with much trauma and blood loss, in order to secure the renal pedicle At times like these we have usually asked ourselves if the procedure has been worth while, and if not, how could it have been avoided When we have operative deaths, or the patient dies shortly after leaving the hospital, particularly when he has tolerated the presence of a tumor for a year or more, has our treatment really been of benefit? It seems worthwhile at times, in order to assure progress in our management of kidney tumors, to appraise our past experiences and try to profit from them Since urothelial tumors and Wilms' tumors behave differently from those of the adult parenchyma, they were not included in this study

STUDY AND MATERIAL

One hundred two consecutive Barnes Hospital cases were reviewed None later than 1949 was included, in order to afford adequate followups The group included 82 males and 20 females The average age was 55 6 years, the youngest being 24 and the oldest 82 The tumor was on the left side in 43 cases, and on the right side in 59

Only cases in which pathology specimens were available for study were included Only three of the 102 cases had inadequate followups (less than 4 years)

TREATMENT

Nephrectomy alone, 48 cases Of these, 46 were done through flank incisions and two transperitoneally There were 6 postoperative deaths (12 5 per cent)

Nephrectomy with x-ray therapy pre- or postoperatively, 27 cases All of these were operated on through flank incisions There were 2 postoperative deaths (7 4 per cent)

Biopsy followed by x-ray therapy, 6 cases The average dosage was 3700 r u , and it varied from 1656 to 4800 r u Two portals were used in 3 cases, and three portals in the other three There was one postoperative death

Biopsy only, 9 cases There was one postoperative death

X-ray only without preliminary biopsy, 1 case

No treatment in the hospital, 11 cases The diagnosis was made at autopsy

RESULTS

Of the 102 cases included in this series, eleven received no therapy Some of these entered in extremis and in some the diagnosis was made at autopsy, the patient having died of some other disease

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Read at annual meeting South Central Section of American Urological Association, Colorado Springs Colo October 18 20 1954

TABLE 4. *Postoperative deaths*

	Age	Operation	Operative Complications	Cause of Death	Time Post-Op.	Curable
1	52	Nephrectomy rt.	None	Shock and hemorrhage	3rd day	Yes
2	68	Nephrectomy rt.	Massive local extension	Shock and hemorrhage	24 hrs.	No
3	62	Nephrectomy rt.	Perinephritis	Shock and hemorrhage	12 hrs.	Yes
4	46	Nephrectomy rt.	Local extension	Aspiration pneumonia	3rd day	No
5	68	Nephrectomy left	Local extension	Ataleetasis and pneumonia	3rd day	No
6	56	Nephrectomy left	Local fixation Hemorrhage	Shock and hemorrhage	8 hrs.	No
7	55	Nephrectomy rt.	Uncontrollable shock	Shock	4 hrs.	Yes
8	24	Nephrectomy left	Massive local extension	Evisceration	13 days	No
9	65	Kidney biopsy	Massive local extension	Shock	12 hrs.	No
10	49	Kidney biopsy	Massive local extension	Sepsis	8 days	No
11	60	Kidney biopsy	Massive local extension	Sepsis	3 days	No

DEATHS

There were 81 known deaths. The remaining 21 patients are either still alive or lost.

Sixty-six patients died of carcinomatosis. Thirteen of these were confirmed by autopsy. The other 53 patients were known to have had recurrences, but died at home or at some other hospital. These deaths were apparently due to carcinoma.

There were eleven postoperative deaths (table 4).

Six deaths were due primarily to shock and hemorrhage. Four of these followed particularly difficult and bloody operations, in spite of apparently adequate blood replacement. They never recovered from the initial operative shock. The other 2 deaths followed massive postoperative hemorrhages. In one of these the wound was reopened and packed, but the patient still died of shock a few hours later. The other died before the wound could be reopened. At autopsy the ligature was found to have slipped off the renal pedicle.

Three of these 6 cases had no evidence of metastasis in the chest films, and no local extension of the tumor, and thus would probably have been cured if they had survived the operation.

One patient died of atelectasis and secondary pneumonia on the third postoperative day.

One patient died of aspiration pneumonia on the third postoperative day.

One patient died 4 days following a wound disruption and secondary closure. This is one of the two cases in which a transperitoneal approach was used through a paramedian incision.

Two patients were found at operation to be grossly inoperable, and only biopsies were done. They died of sepsis on the third and eighth postoperative days, respectively. At autopsy both were found to have had pyonephrosis and perinephric abscesses. Though each incision had been drained, the drainage apparently was not adequate. Their poor general condition preoperatively also apparently contributed to the fatal outcome.

Though none of these cases had demonstrable metastases on preoperative x-ray studies, eight of the tumors were found at operation to have spread beyond the limits of adequate surgical excision. The perirenal fixation due to tumor extension made nephrectomy quite difficult and bloody, thus being directly responsible for 3 cases lost from shock and hemorrhage. These deaths might have been avoided if it had been possible to stop the operation as soon as it became apparent that the tumor could not be removed. This was not possible, however, because hemostasis could be obtained only by securing the renal pedicle. A nephrectomy then had to be done in desperate haste by cutting through the tumor before exsanguination occurred.

Three of the patients dying of postoperative shock and hemorrhage were apparently cases that could have been cured. Two of these deaths were due to inadequate ligation of the renal pedicle. We feel that the pedicle should be freed as much as possible of extraneous tissue and then doubly ligated, the distal ligature being transfixed.

The death due to aspiration pneumonia might possibly have been avoided by prompt suction as soon as the vomitus was aspirated, or, better, by preventing the aspiration by turning the semi-anesthetized patient on his side when he began to vomit.

Death from atelectasis can usually be avoided by promoting complete aeration of both lungs as soon postoperatively as possible by coughing and deep breathing.

The 2 deaths due to sepsis might have been prevented by more adequate drainage. Both of these patients were found to have extensive carcinomatosis, however, and were in poor general condition before operation. The sepsis thus could have been due to poor resistance to infection. We were impressed in this series of cases with the frequent association of infection (pyonephrosis and perinephritis) and kidney tumors.

Four patients were known to have died of other disease. One had a stroke, two had coronary occlusion, and one died apparently of old age (86) 13 years after operation. He had no evidence of recurrence when last seen 2 years before his death.

LOCAL RECURRENCE

Since most of the patients did not re-enter the hospital following operation, there were probably other local recurrences concerning which we do not know. Eight who had nephrectomy did return to the hospital, however, with local recurrence. Since the kidney tumor was not fractured during its removal it is presumed that local extension had already occurred at the time of operation. Some of the recurrences appeared late (average 30 months postoperatively). Our data are inaccurate in that we do not know how long the recurrence was present be-

TABLE 5

Post-operative Deaths		Number of Cases	5 Year Survivals	Still Alive Over 5 Yrs.	Lost	Average Known Survival
5	Clear cell	62	15	11	2	36 mos.
3	Mixed clear and granular cell	22	5	5	1	33 mos.
2	Mixed undifferentiated and renal cell carcinoma	15	0	0	0	4.3 mos.
1	Carcinoma and sarcoma	3	0	0	0	2.0 mos.
		102	20	16	3	

fore it was first noticed by the patient. One appeared 5½ years after nephrectomy, a brain metastasis having been removed during the fourth year. Once a recurrence became apparent, death soon followed (7 months average).

Of particular interest were 5 cases in which the kidney tumor was broken open during operation, and tumor spilled grossly into the wound. None of these had evidence of metastasis or local spread. In one of these, no followup data could be obtained. Three of the other four, however, are still alive and free of tumor (7½ years or more after operation). The fourth one died 8 months postoperatively of a brain metastasis, but no local recurrence could be found at autopsy. None of these received x-ray therapy. Thus, in this series, recurrences developed only in cases in which the tumor had already spread. There were no recurrences from tumor implantation, i.e., wound contamination.

FACTORS INFLUENCING SURVIVAL

Type of tumor. Many of the tumors, if studied thoroughly (table 5) contained more than one cell type. In 62 of the tumors only the clear cell type was identified (fig. 1, *A*). No purely granular cell carcinomas were found (fig. 1, *B*).

The prognosis of the differentiated tumors (clear and granular cell types) was relatively good; all of the 5-year survivals were with tumors of these types. Their average survival was 35 months.

None of the patients with undifferentiated carcinomas (15) survived the first year, and their average survival was only 4.3 months (fig. 2, *B*).

The patients with sarcomas (3) had the poorest survival of all (2 months). None of them survived the first 6 months (fig. 2, *A*).

Seventy five per cent of the metastases were apparently blood borne (lungs, brain and bone) and only 25 per cent were by way of lymphatics (local lymph node metastasis).

Size of tumor. The average weight of the removed specimens (kidney plus tumor) was 644 gm. The size of the tumor seemed to have a fairly close relationship to prognosis. The cases with smaller tumors (less than 600 gm.) had an average survival of 40 months, compared to 18 months for those with larger ones (over 600 gm.).

Presence of preoperative metastasis. Of the 16 cases with metastasis noted preoperatively on the chest film, the average survival was only 7 months. The longest survival was 37 months. Two patients had normal chest films but were

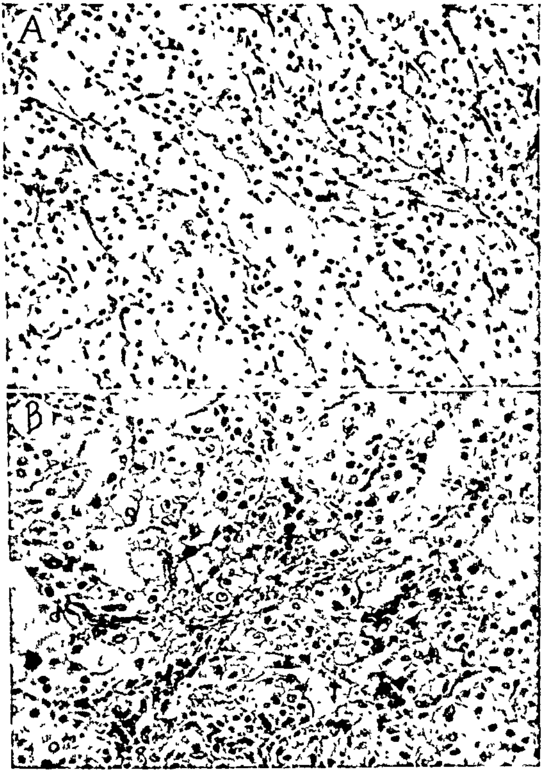

FIG 1. Renal cell carcinoma. *A*, clear cell type. *B*, granular cell type

known to have had metastases elsewhere preoperatively. Their average survival was only 5.3 months. The overall survival for cases known to have metastases preoperatively was only 6.7 months.

Local extension. Twenty-seven patients had local extension of tumor outside the kidney at the time of operation. Their chest films were normal Their average survival was only 5.7 months (none longer than 14 months). Ten cases had vein invasion in addition to local extension of tumor outside the kidney. These had an average survival of 7.1 months.

Four cases had vein invasion as the only evidence of tumor spread. Two of these had gross tumor thrombi in the renal vein with survivals of 4 and 10 months, respectively. The other 2 cases, however, had invasion only of the small intrarenal veins in the vicinity of the tumor. These two are still alive 5 and 12 years after operation, and are free of recurrences. They did not receive x-ray therapy.

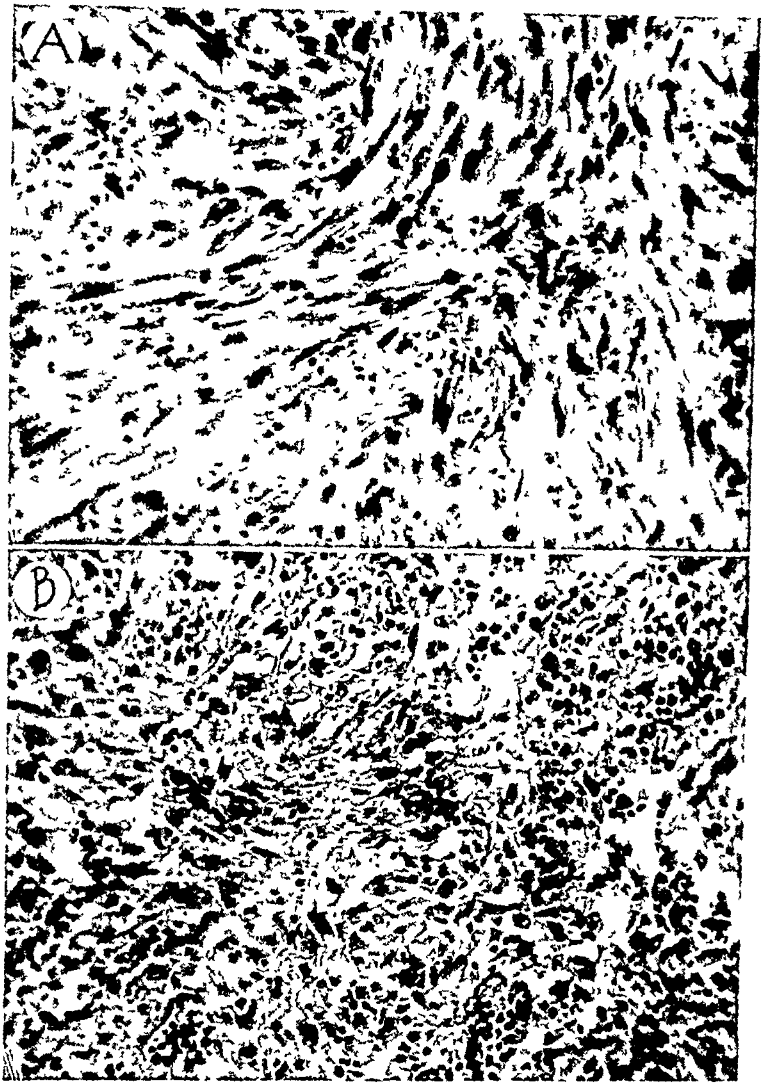

FIG. 2. *A*, undifferentiated carcinoma of kidney. *B*, sarcona of kidney

Thus we have had no success in cases with distal or local tumor spread. Though tumor thrombi in the renal vein were fatal in both of the 2 cases reported here, invasion of the smaller renal vessels is of doubtful significance in view of the fact that in the 2 cases noted the patients have apparently been cured without benefit of x-ray therapy.

Symptoms. See table 6.

The average recorded duration of symptoms was 15.5 months. Those with symptoms less than 1 year survived an average of 31 months after operation, compared to 27 months for those with symptoms over 1 year. Thus there was no apparent relationship between duration of symptoms and survival.

Except for hematuria, the usual symptoms of flank pain, weight loss, and mass have little prognostic significance (table 6). Symptoms suggestive of metastasis, however (chest symptoms, headache, and pain other than in the kidney region) and weakness seem to carry a particularly grave prognosis (average survivals 1 to 12.5 months).

TABLE 6 *Initial symptoms*

Initial Symptom	No Cases	Average Duration (months)	Average Post operative Survival (months)
Hematuria	38	15.5	39
Flank pain	20	21.8	21.5
Weight loss	14	1.9	28
Weakness	8	17	12.5
Mass	5	12	53
Dyspnea and pleurisy	3	9	5.7
Dysuria	2	9	58
Headache	2	12	2
Cough	2	10.5	5.5
Fainting	1	12	72
Pain in thigh or back	2	9	5
Abdominal pain or distention	2	66	1
Fever	1	36	2
In extremis	2		
	102		

Dilated perirenal veins Thirteen operative notes mentioned large perirenal veins having been encountered Eleven of these were found to have local extension of tumor outside the kidney and/or vein invasion The dilated veins were apparently due to occlusion of the renal vein by tumor thrombus (5 cases) or by extrinsic pressure of the tumor on the renal vein The two tumors showing no evidence of vein invasion or local tumor spread were unusually large, and it is likely that their size alone was responsible for the large peripheral vessels by hindering the venous return from the tumor One of these latter patients survived 7 years before dying of a brain metastasis

Other than for the one 7-year survival, the outcome was very poor (average survival for the remaining 12 cases was only 6 months) There were three postoperative deaths in this group, all due to shock and hemorrhage, thus attesting to the operative difficulty under these circumstances

Age of patient Because of the small number of cases in some of the groups (table 7), no definite relationship between age and prognosis can be demonstrated

Perirenal adhesions (fixation) At nephrectomy the kidney was found adherent to the perirenal tissue in 35 cases The fixation in thirteen was found to be due to perinephritis (fig 3) rather than to extrarenal extension of the tumor These

TABLE 7 *Relationship of age of patient to prognosis*

Age	Number of Cases	Average Survival
20–30	2	1 mo
31–40	4	29 mos
41–50	25	39 mos
51–60	31	34 mos
61–70	25	24 mos
71–80	4	69 mos

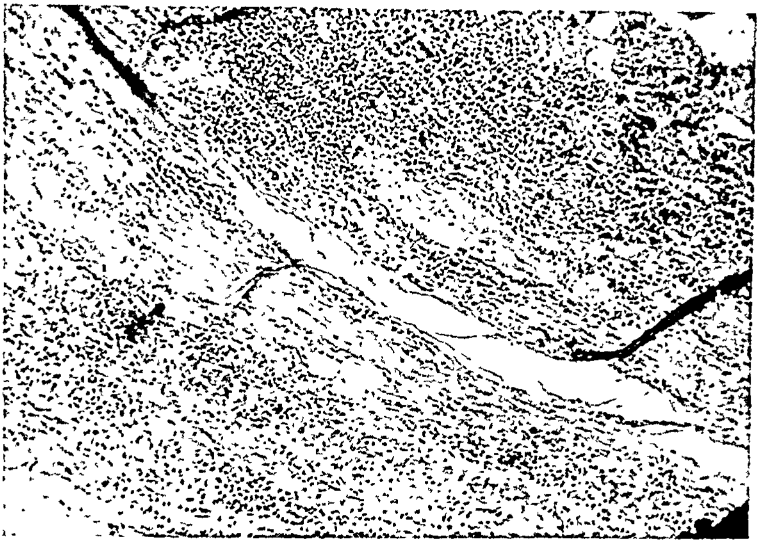

FIG. 3. Carcinoma of kidney with perinephritis

13 cases had an average survival of 67 months, and five of them lived 5 years or more. Thus, a fixed kidney is not necessarily due to tumor spread.

Era when surgery was done. Ten of the 11 postoperative deaths occurred prior to 1943. This represented an 18 per cent mortality for the 55 patients operated on during that period. From January 1943 through 1949 only 1 postoperative death occurred in 47 cases (2.2 per cent). The improvement in operative mortality has apparently been due to better pre- and postoperative care, better anesthesia and more available blood for transfusions.

DISCUSSION

The main stimulus for this study has been the recurring occasion when in the operating room we have found ourselves unable to remove a kidney tumor and unable to control the hemorrhage and terminate the procedure. Or we have operated upon someone who has obviously had and tolerated a tumor a number of years with relative comfort, only to have him die a few months later without ever having recovered from the morbidity of the operation. It seems that both of these unfortunate situations should be, to a greater extent, avoidable. None of the 28 nephrectomies performed on inoperable cases proved to be of any benefit. Twelve of these cases were known preoperatively to have had metastases. The nephrectomy was done to remove the objectionable tumor mass. In a few cases a faint hope of cure was entertained on the basis of Mann's report on the disappearance of metastases following removal of the primary tumor. Seventy two per cent died within the first year, 93 per cent by the end of the second year, and the remainder in less than three years. Noteworthy, also, is the fact that five of the eight postoperative deaths following nephrectomy occurred in these 28 cases.

All of the nephrectomies were performed through the regular flank incision except for two which were done transperitoneally through rectus incisions. Usually, when the flank incision is used, most of the kidney must be freed before the pedicle can be adequately visualized. Often the inoperable condition of the kidney is not recognized until the pedicle is approached and extrarenal tumor is encountered. By this time, bleeding from perirenal vessels is often so profuse that it can be controlled only by securing the renal pedicle. The normal planes of dissection are usually obliterated by the tumor so that, in desperate haste, we must clamp and cut across inadequately identified tissue until the kidney specimen is free. Such blind dissection is likely to injure the duodenum, vena cava, or other vital structures, and change the unfortunate condition into a catastrophic one. Next comes the problem of ligating renal vessels that have not been adequately freed from the surrounding tumor, or worse, not even identified. Such ligatures are much more likely to lose their purchase on the renal vessels postoperatively, and are always regarded with considerable apprehension until this danger is past.

We feel that the usual flank incision affords inadequate exposure when a large and/or fixed tumor of the kidney is to be removed. The transperitoneal exposure, in our experience, has been equally unsatisfactory. Lately we have been using the thoracoabdominal approach, as described by Dr. Richard Chute, on our more difficult cases, with great satisfaction. Dr. Chute's enthusiasm for this procedure is well founded. By using it, we have been able to inspect the vicinity of the renal pedicle and vena cava before freeing the kidney and starting significant bleeding. At this point in the operation it is still possible, if the tumor is found to be inoperable, to terminate the procedure without having to perform a bloody, useless nephrectomy. On the other hand, if the tumor seems operable at this point, the pedicle can usually be secured and divided before having to mobilize the kidney. The kidney and its surrounding tissue can then be removed *en bloc*, along with the perirenal fascia. Five of the eight postoperative deaths following nephrectomy occurred in inoperable cases. Some of them could possibly have been prevented if 1) it had been possible to terminate the procedure as soon as the hopeless condition was recognized, or 2) if the superior thoracoabdominal exposure had been available for securing the renal pedicle before excessive hemorrhage occurred.

Local recurrence was apparently due to inadequate removal of tumor rather than to tumor spillage and implantation.

Ordinary x-ray therapy had no apparent effect on these tumors. The outcome of comparable cases in this series which did or did not receive radiation therapy was almost identical. The effect of supervoltage x-ray has not yet been evaluated.

One is often tempted, when treating an obviously hopeless case, to try desperate, foolhardy measures. This would seem to be the result of emotional rather than rational thinking. It is sometimes reasoned that these patients have nothing to lose. The fallacy of this concept seems well borne out by the high operative mortality, the high postoperative morbidity, and short survival. There were no exceptions to this course in our series. Occasionally, however, an inoperable kidney tumor must be removed in order to stop uncontrollable bleeding.

It would seem that before a kidney is removed, the patient should have a very extensive examination to determine the operability of the tumor. If there is local fixation, or if the tumor is quite large, this study should be especially

FIG. 4. Venacavagram, normal

thorough. In the past 3 years we have done two venacavagrams by injecting 70 per cent urokon into the femoral vein in an attempt to demonstrate tumor thrombi in the vena cava. Both were negative (fig. 4), but perhaps it will some day prevent a futile operation. In doubtful cases we should try to postpone the decision as to whether or not to remove the kidney until the operative condition can be as satisfactorily appraised as possible, even to the extent of exposing and inspecting the renal pedicle and surrounding structures.

Certainly, every prospective patient with a kidney tumor should at least have a chest film or a series of films to determine the presence of metastases before being subjected to operation.

SUMMARY

One hundred two consecutive cases of malignant parenchymal tumors of the kidney in adults were reviewed and analysed.

The series included 82 male and 20 female patients.

Seventy-five nephrectomies were done. Twenty-seven of these patients received supplemental x-ray therapy.

There were 11 postoperative deaths (eight following nephrectomy).

There were twenty (22 per cent) 5-year survivals and sixteen (18 per cent) apparent cures

X-ray therapy proved to be of no benefit in these cases

Twenty-eight nephrectomies were done on incurable patients Twelve of these were known preoperatively to have had metastases The results in these cases were all bad

Local recurrences were apparently due to preoperative tumor spread rather than to implantation of tumor in the wound at the time of operation

The well-differentiated tumors had a much better prognosis than the poorly differentiated ones

The smaller tumors had a much better prognosis than the larger ones

There was no apparent relationship between the duration of symptoms preoperatively and prognosis

Weakness and symptoms indicating distant metastasis were of grave prognostic significance

The presence of dilated perirenal veins was usually associated with an inoperable tumor

The age of the patient had no significant influence on prognosis

Perirenal fixation was due to perinephritis rather than tumor extension in approximately one third of the cases

The postoperative mortality prior to 1943 was 18 per cent (10 out of 55 cases operated) compared to only 2 per cent for the 17 later cases This apparently reflects better pre- and postoperative care, better anesthesia and better availability of blood for transfusions

CONCLUSIONS

Since approximately one-third of the nephrectomies were performed on inoperable cases, more thorough preoperative studies seem indicated Removal of kidney tumors which have already spread not only has proved to be of no benefit, but seems to have shortened the life of many of the patients

An improvement in operative exposure and technique in order to obtain earlier and better hemostasis is indicated The thoracoabdominal approach is far superior to the regular flank and transperitoneal approaches in these respects, and should be employed more often

We wish to thank Dr L V Ackerman, professor of surgical pathology, Washington University School of Medicine, for reviewing the pathological material with us, and helping in the preparation of this study

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NEPHRECTOMY FOR CARCINOMA SEVEN YEARS AFTER DEMONSTRATION OF THE TUMOR

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A particularly unique set of circumstances existed in the case herein described, allowing removal of a kidney bearing a carcinoma 7 years after its demonstration on roentgenograms investigating the gastro-intestinal tract. The presence of calcification within the malignant growth and the incidental finding of multiple adenomas elsewhere in the removed kidney further warrant recording this single case.

CASE REPORT

A white man aged 44 (No. B23309) was first seen in the New Haven Hospital Dispensary on January 6, 1942. His only complaint was epigastric burning pain of several months' duration. The absence of any urinary symptoms was noted and recorded. The only significant positive physical finding was slight tenderness in the midepigastrium and right hypochondrium. The blood pressure was 140/90. His weight was 142 pounds. A complete blood count was normal. A urine analysis was normal except for 1 plus albumin; no red blood cells were noted in the sediment. A subsequent urine analysis was negative. A diagnosis of gastritis was made and symptomatic treatment prescribed. Only partial relief of the epigastric distress had been obtained 2 weeks later and roentgenographic studies were requested. The preliminary film of the abdomen disclosed a homogeneous round density overlying the lower pole of the right kidney. Examination of the entire gastro-intestinal tract after the administration of barium was negative except for the presence of coarsened gastric rugal markings. A cholecystogram was normal except for the mass just described (fig. 1). Because of the persistence of the epigastric distress, a gastroscopic examination was performed on February 13, 1942, revealing chronic hypertrophic gastritis and a healing erosion of the lesser curvature. After modification of the dietary and medical regimen, prompt relief was obtained. He was seen at regular intervals during the next 3 months without recurrence of symptoms. In August 1942, the patient entered the hospital for an uneventful repair of a right inguinal hernia. No further investigation of the right upper quadrant mass noted on the roentgenograms was made.

The patient enjoyed good health until January 31, 1949, when he experienced slight dysuria on passing some red, cloudy urine. Although the symptoms had subsided, he consulted his physician the next day and microscopic hematuria was detected. He was then referred to the urological service of the New Haven Hospital for additional studies. The only pertinent physical findings were elicited on examination of the abdomen. There was a definite fullness of the right upper quadrant as compared to the left; no mass could be palpated. Deep pressure disclosed moderate tenderness over the right hypochondrium. The blood pressure

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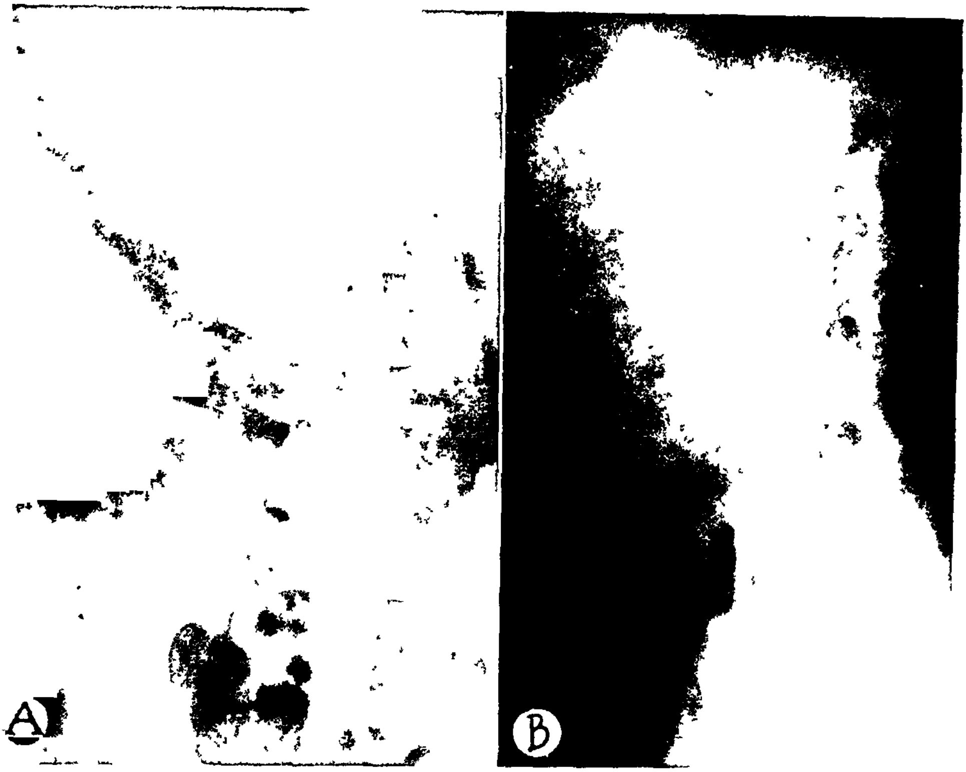


FIG. 2. *A*, film made in 1949 reveals considerable increase in size of mass with some calcific deposits. *B*, lateral view of right retrograde pyelogram showing slight pressure on inferior calyces and displacement of proximal ureter.

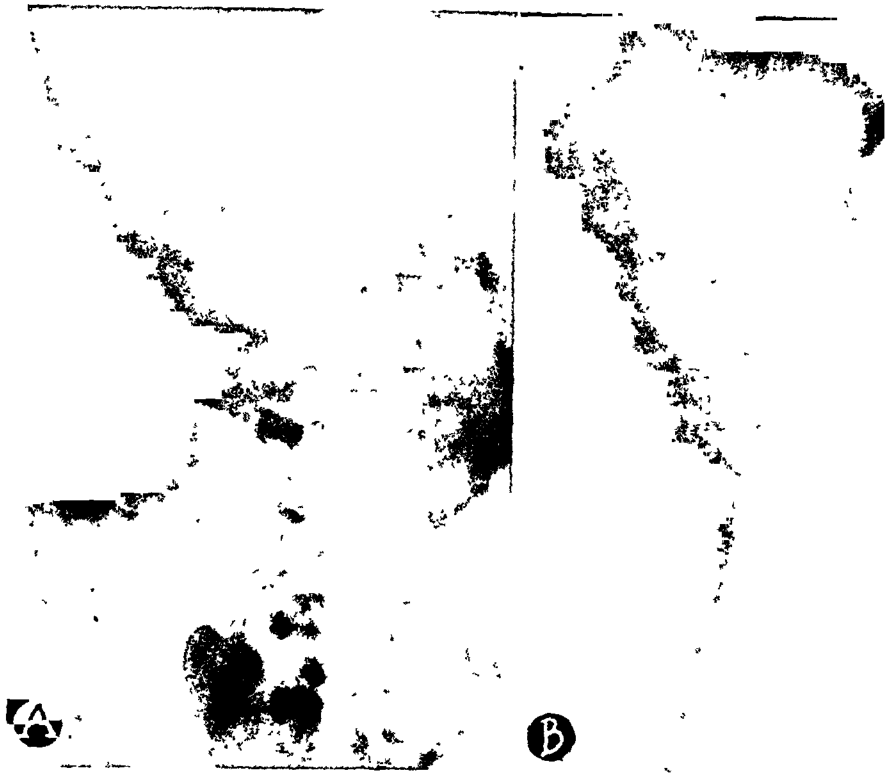
capsular cysts, measuring up to 1 cm. in diameter, containing a clear, colorless fluid. There was no apparent neoplastic involvement of the hilar vessels. The proximal 8 cm. of the ureter was attached and was not remarkable. The tumor cut with a grating sensation, revealing irregular calcific deposits around its periphery. The growth was sharply demarcated from the kidney proper; its surfaces were variegated yellow-red (Fig. 3). Hemorrhagic areas were numerous. The central portion was filled with a thick, red-brown liquid in which glistening minute yellow crystals were apparent. Near the periphery, the neoplastic tissue was somewhat more firm. The cut surfaces of the kidney proper were light red-brown, firm and did not bulge. Minute gray-white streaks were noted in the pitted areas around the periphery of the cortex. The lining of the cysts was thin and glistening; in some, there was a thin layer of soft yellow tissue between the lining and the adjacent renal parenchyma. Scattered throughout the cortex, there were minute gray-yellow spots measuring up to 0.3 cm. in diameter. The pelvis and inferior calyces were slightly compressed by the tumor. The mucosal surfaces of the calyces, pelvis and ureter were glistening and unremarkable except for a 0.5 cm. defect on the medial aspect of the midportion of the pelvis where the growth had eroded into the lumen.

Microscopic preparations, stained with hematoxylin and eosin, disclosed the growth in the lower pole to be a carcinoma composed of papillary projections covered by tall columnar cells with basally placed, deeply stained nuclei (fig. 4, was 140/80. He did not have fever. His weight was 140 pounds. Examination of a catheterized urine specimen was negative except for the presence in the sediment of 1 to 3 red blood cells per high power field. A second specimen examined later revealed many red blood cells in the sediment. A blood count revealed 4,470,000 red blood cells; the hemoglobin content was 14 gm. per 100 cc; there were 10,300 white blood cells with a normal differential count. A Mazzini test was negative. The blood nonprotein nitrogen was 41 mg. per 100 cc and the serum protein determination was 7.5 gm. per 100 cc. The phenosulfonpthalein test disclosed 45 per cent excretion in the first hour and an additional 15 per cent in the second hour. Calcification of the periphery of a round mass adjacent to the lower pole of the right kidney was noted in a scout film (fig. 2, *A*). A cystoscopic examination was performed and retrograde pyelographic studies carried out. No distortion of the drainage system was noted except in the lateral view which disclosed posterior displacement of the proximal ureter by the mass (fig. 2, *B*). Excretory urography revealed prompt function by both kidneys. The left kidney appeared normal. A roentgenographic metastatic survey was negative.

FIG. 1. Cholecystogram performed in 1942 disclosing round soft tissue mass posterior to superior half of gallbladder.

On February 15, 1949, a right nephrectomy and partial ureterectomy were performed. After induction of general anesthesia, it was not possible to palpate a tumor through the relaxed abdominal wall. After resection of the twelfth rib, the kidney containing a tumor on the anterior surface of the inferior pole was delivered without difficulty. The postoperative course was uneventful except for atelectasis of the lower lobe of the left lung on the first postoperative day. This responded promptly to treatment. The operative wound healed per primam. His course was afebrile after the brief pulmonary complication and he was discharged from the hospital on the tenth postoperative day.

The operative specimen consisted of the right kidney which measured 12 by 7 by 4.5 cm. and weighed 363 gm. A spherical, red-gray mass, 7 cm. in diameter, projected from the anteromedial surface of the inferior pole; its external surface was quite firm. The surface of the kidney proper was irregularly pitted with its capsule in places thickened and gray-white. There were several thin-walled sub-



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Microscopic preparations, stained with hem
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similar to the case described here where the roentgenographic appearance led to the erroneous diagnosis of calcified mesenteric cyst Knowledge of the occurrence of this degenerative change within renal carcinomas aids in the differential diagnosis of this and other conditions including renal lithiasis and tuberculosis, simple renal cysts, echinococcus cysts, calcified lesions of the liver and spleen, retroperitoneal cysts and neoplasms, and calcification within old hematomas When present in neoplasms, these deposits of calcium are usually found in the slower growing tumors, as in the case described here However, even the slowest growing renal carcinomas eventuate in widespread metastases and death Thus, it is not surprising that in the 12 cases of calcification within renal carcinomas described by Cahill and Melicow,[1] only one of the patients lived as long as 2 years

The development of adenomas secondary to arteriosclerotic changes in the kidney has long been known to pathologists[4, 5] Since the scarring, atrophy and cyst formation resulting from vascular occlusion do not constitute a surgical entity, the great majority of renal adenomas are incidental findings, either in kidneys removed surgically or at necropsy Most renal adenomas are quite small and their incidence is directly proportional to the care exercised in examining the gross specimen Only brief mention or none at all is accorded these growths in most textbooks of surgery and surgical pathology Their clinical significance pertains to their relation, if any, to the development of renal carcinomas The chief problem encountered by the pathologist is the morphologic distinction between carcinomas and the larger solitary adenomas which are usually found in otherwise normal kidneys The clinical course following removal of such growths occasionally settles the issue when metastases from an "adenoma" bring about the death of the patient The knowledge of the existence of renal adenomas or the co occurrence of adenoma and carcinoma in the same kidney does not allow the conclusion that the malignant growth results from the transformation of the benign tumor As suggested by Cabot and Middelton,[6] the same forces initiating the formation of the adenoma may also initiate the formation of a carcinoma It is generally agreed that small, multiple adenomas of the type discovered in the case reported here do not predispose to carcinoma The long known duration of the carcinoma before it was removed at the age of 51 suggests that the malignant neoplastic process may have preceded the degenerative arteriosclerotic changes and the development of the adenomas

SUMMARY

Nephrectomy for carcinoma and incidental multiple adenomas 7 years after roentgenographic demonstration of the malignant tumor is reported in a white man, 51 years old at the time of operation Shell like calcification of the periphery of the carcinoma developed in the period between examinations The patient is alive and well over 5 years after operation The significance of renal adenomas and calcification within renal carcinomas is briefly discussed

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HEMANGIOPERICYTOMA: REPORT OF A CASE INVOLVING THE KIDNEY

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The term, hemangiopericytoma was originated in 1942 by Stout and Murray in order to name a tumor arising from the capillary pericytes.[1] These cells, according to the Swiss histologist Zimmermann, are contractile cells of modified smooth muscle which encircle the capillary and serve to change the caliber of its lumen.[2] This type tumor has been variously described as fibrosarcoma, angiosarcoma, periendothelioma, simple cell sarcoma, and others.[3-4]

We have been able to find only 38 cases reported in the literature to date and, although several have occurred in the retroperitoneal space, this is the first to be reported involving the kidney.[5-6] Though knowledge of the characteristics and activity of this tumor is as yet meager, we can confirm, even with our limited experience, many of the opinions expressed elsewhere concerning hemangiopericytoma.

The gross appearance is not sufficiently characteristic for clinical recognition; however it is usually very firm and often appears to be encapsulated. It tends to grow locally and is slowly progressive. It may, however, infiltrate the surrounding tissues. Fortunately, the incidence and degree of malignancy appear to be low, but occasionally it has demonstrated rapid infiltration and distant metastasis. The majority of cases have been in younger individuals and have been most often located in the superficial tissues.[6, 7, 8] Thirty-eight cases have been reported in various locations including the thoracic, abdominal, and pelvic cavities.[6, 9-13]

Read at annual meeting, South Central Section of American Urological Association, Colorado Springs, Colo. October 18–20, 1954.

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Final diagnosis must be made histologically. Hematoxylin and eosin stain are often satisfactory, however diagnosis is greatly facilitated by Laidlaw's silver reticulin stain.[1-8] According to Stout, histologically hemangiopericytoma is a vascular tumor composed of a profusion of endothelial lined capillaries which are surrounded by rounded to elongated cells in a supporting reticulum meshwork.[1-6] The cells are always on the outer wall of the capillaries, and they may be so closely packed that often the capillaries are difficult to detect without silver stain. Quite often the apparent capsule shows tumor formation, however this does not appear to make the prognosis more grave.

CASE REPORT

M. H. No. 78612, a white, married housewife, 29 years of age, entered Saint Louis City Hospital July 31, 1953, complaining of severe nausea, vomiting, diarrhea, and pain in the right lower quadrant. On the morning of July 31, the patient awoke with the desire to void. She noted "vaginal bleeding," followed by the rapid onset of severe cramping pain in the right lower quadrant which radiated to the right lumbar region and the right costovertebral angle. This pain was accompanied by nausea and vomiting, and within a few hours, severe diarrhea developed. There was no frequency or dysuria.

On July 10, 1953, the patient experienced a similar episode of "spotty vaginal bleeding" with nausea, vomiting, and pain in the right side similar to that on admission. These symptoms had lasted for 4 or 5 days before abating. No genitourinary symptoms were noted with this episode.

The temperature on admission was 105F; the pulse, 120/min.; and the blood pressure, 70/40. There was moderate tenderness to palpation over the right upper and lower quadrants, with rebound tenderness over the right upper quadrant. The bowel sounds were active. Other findings were felt to be negative, however, on August 2, 1953, the gynecological consultant felt that the cervix was enlarged, bluish, and that a foul-smelling, thin, reddish discharge was coming from the cervical os. A diagnosis of endometrititis, with bacteremia and generalized sepsis, was made. Treatment primarily with antibiotics and supportive measures was instituted.

The patient's urine on admission contained red and white blood cells too numerous to count. Blood urea nitrogen at this time was 37 mg. per cent. The white blood cell count was 23,250, and the hemoglobin was 14 gm. Cultures of the blood, urine, and cervical discharge were positive for E. coli.

On August 1, 1953, a flat film of the abdomen revealed a large, rounded mass in the region of the lower pole of the right kidney. The bladder was mildly inflamed with a small amount of whitish exudate present over the trigone. A No. 5 ureteral catheter was passed up the right ureter without difficulty. A right retrograde pyelogram revealed pelvic distortion, abnormal kidney position, and the presence of a mass of the lower pole (fig. 1). Later excretory urograms revealed good function bilaterally.

The patient had a shock-like course which necessitated the use of vasopressors for 3 days after admission. She responded slowly to antibiotics and supportive care. The urinary output was low for the first 5 days with the blood urea nitrogen

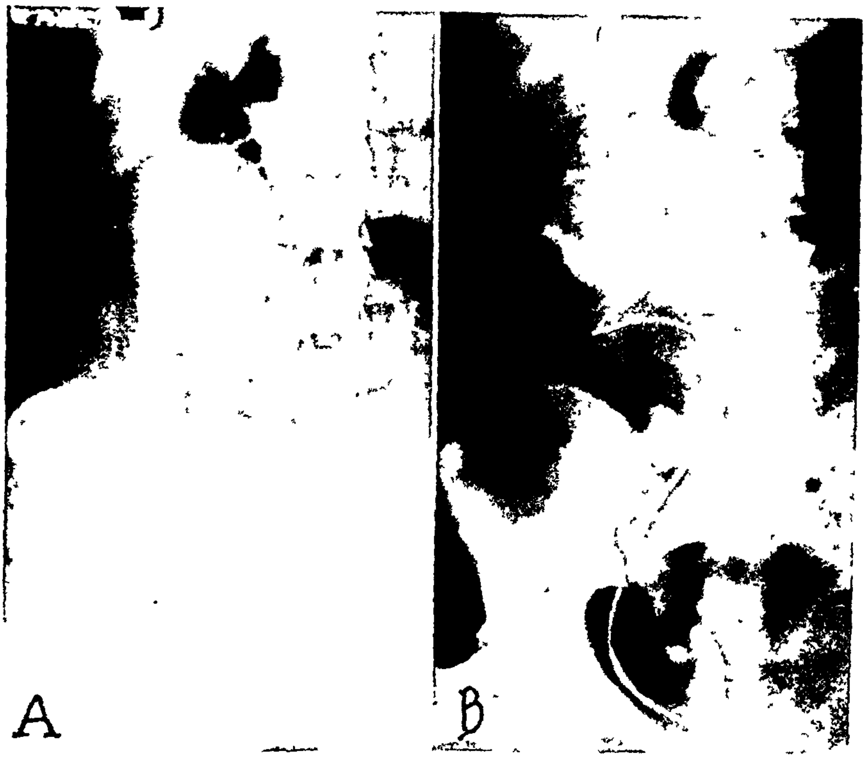

FIG. 1 *A*, plain x-ray showing large mass in region of lower pole of kidney. *B*, right retrograde pyelogram showing abnormal kidney position, presence of mass and distortion of renal pelvis.

rising to 140 mg. per cent, then falling to 24 mg. per cent over a period of the next 30 days. Microscopically, the urine slowly cleared. Further roentgenological studies continued to show an unchanging mass of the lower pole of the right kidney. It was felt that the second portion of the duodenum was pushed medialward by this mass. The patient refused further diagnostic or operative procedures at the time. On September 1, gross hematuria developed and continued without change until September 9, at which time the patient started passing clots with considerable colicky pain on the right. At this point the patient agreed to surgery.

On September 13, a right nephrectomy was done through a flank incision. The kidney was exposed without difficulty, and it was found to have a firm, rounded, slightly nodular, bilobed mass attached to its medial and lower border. This mass was freed easily from surrounding fatty tissue and was felt to be encapsulated. The kidney and attached mass were removed without difficulty. There was no evidence of extension of the tumor.

Pathology report (No. 58472): Gross inspection revealed a normal-appearing kidney with a tumor closely attached to, or arising from, the anteriomedial aspect. The tumor was firm and lobulated, measured 14 by 9 by 9 cm., and seemed to be well capsulated. The inferior portion of the tumor had the consistency and appearance of renal tissue, however, the upper portion was very firm and of a mottled color which varied from reddish-brown to yellow. The ureter, artery, and vein passed anteriorly to the tumor, and did not appear to be involved. The pelvis was densely adherent to the tumor. The tumor was supplied and drained by large branches of the renal artery and vein.

The cut surface of the kidney was not unusual, however, the mucosa of the pelvis was hemorrhagic and revealed superficial erosions over the adherent tumor. The tumor was primarily extrarenal except for a 2 by 1 cm. point of junction.

The cut surface of the inferior portion of the tumor resembled renal parenchyma with several small, firm, yellow areas scattered throughout. The cut surface of the upper portion showed some areas which were firm and from yellow to pink in color, and other areas which were reddish-brown and necrotic. There was no evidence of extreme vascularity.

Microscopic examination (fig. 2): "The tumor is made up of spindle-shaped

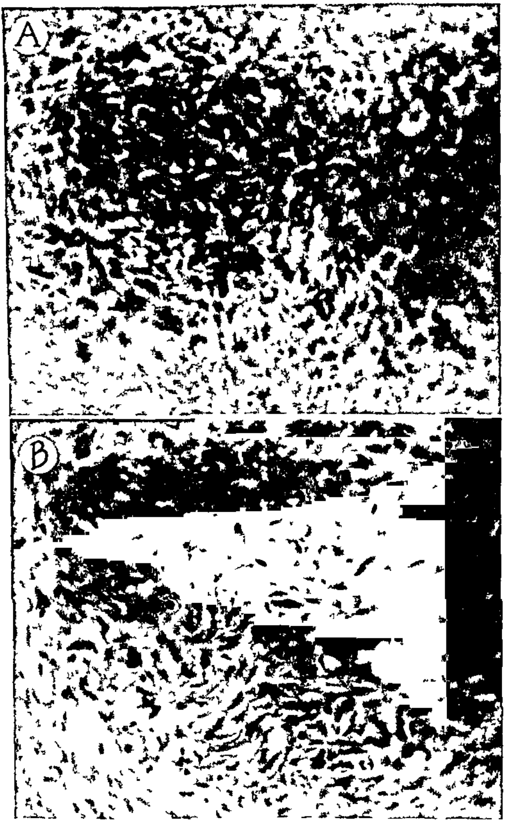

FIG 2 Photomicrographs of renal tumor made from slides stained with hematoxylin and eosin

cells, usually in no particular arrangement, and varying in compactness from dense to myxoid. Large hyalinized areas are present in some places, and there are also areas of necrosis with preservation of the cells only about small vessels. In other areas, capillaries and small vessels are very conspicuous; moreover, the tumor cells appear to form their walls with the exception of a thin layer of lining endothelium. In places, an angiomatous pattern is suggested. A section including the kidney tissue shows continuity, but it is not possible to state whether the tumor is arising from or invading the kidney. The degree of malignancy would appear to be low. Diagnosis: Spindle cell vascular sarcoma, low grade, consistent with hemangiopericytoma." (Signed: J. A. Saxton, M.D., Director of Pathology Department, Saint Louis City Hospital, Saint Louis, Mo.)

The patient recovered rapidly and was discharged. Twelve months after operation, there was no evidence of recurrence.

DISCUSSION

It is not possible to state whether this tumor arose from the kidney parenchyma, or arose from the capsule and invaded the kidney. It did not, however, involve any of the surrounding tissues. The tumor very much resembled a renal cell carcinoma when seen at the time of surgery. Gross appearance is given in detail for information of this type is meager with reference to that type of tumor.

Hemangiopericytomas seem to be slow in growing and this one, since it had obtained such a large size, must have been present for some time.

The urological department was asked for a workup on this patient because of the uncertainty of diagnosis and because of the mass seen in the right kidney region. The possibility that the patient's illness was due to infected abortion, with secondary septicemia, was strongly considered. The pain that the patient experienced on admission may, or may not have been aggravated by the tumor. The July 10 episode may have been due to the tumor, but the only symptom that could be definitely attributed to the tumor was gross hematuria which developed from erosion of the pelvic mucosa over the tumor.

Treatment of this tumor seems to be the same as other renal tumors: early diagnosis and complete removal. Local recurrence seems certain without complete removal. The effect of radiation on this tumor has not as yet been well evaluated.

Prognosis following treatment before metastasis has occurred seems to be very good. It is, of course, enhanced by the fact that the tumor seems slow to metastasize. We feel that this patient's chance of a cure is excellent because of the low grade of malignancy microscopically and the complete removal of the tumor at operation.

CONCLUSIONS

A case of hemangiopericytoma involving the kidney is presented. The clinical and pathological features have been presented. Approximately 38 cases of such tumors have been reported since the lesion was first described in 1942.

In the 12 months since surgery the patient has done well, and there is no evidence of recurrence of the tumor.

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THE RESULTS OF URETERAL TRANSPLANTATION TO A RECTOSIGMOIDAL POUCH

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A review of the early literature on ureterointestinal transplantation readily shows that the original attempts were made to devise a method which would overcome 1) urinary leakage with subsequent peritonitis, 2) obstruction to the ureters, and 3) infection of the urinary tract. The introduction of the direct, or mucosa-to-mucosa technique by Cordonnier and by Nesbit left only leakage as the immediate complication Urinary leakage alone rarely caused difficulties, but fecal drainage was a serious complication in some patients. However, as the surgical technique improved and better measures were developed for control of infection, an increasing number of patients who survived the operative procedure had hyperchloremic acidosis, and this became the major problem. Indeed, Ferris and Odel, and Boyce and Vest have reported that 79 per cent of their patients who had had ureterointestinal anastomosis showed postoperative chronic acidosis.[1, 2]

The mechanism of chronic acidosis following ureterointestinal anastomosis has been demonstrated by many observers to be due in large part to the continuous reabsorption of electrolytes.[3-7] For a long time it has been known that the large intestine is capable of absorbing water, sodium chloride, calcium, glucose, arsenic, atropine, and methylene blue.[8-10] Lapides,[11] along with Doroshow[12] and Cordonnier and Lage[13] have suggested that unrecognized secondary renal damage may also be a contributing factor. Mitchell and Valk[6] have disagreed with this and show statistics that disprove that poor renal tubular function has anything to do with the acidosis Bohne[14] has recently reported a case of severe pyelonephritis and acidosis which was restored to normal electrolyte balance by reimplanting the ureters into the bladder. In other cases, the acidosis has been reportedly corrected by nephrostomy The preponderance of evidence, however, would seem to indicate that reabsorption is the primary factor in producing hyperchloremia and acidosis, with the possibility of renal tubular damage a secondary factor. Pressure changes on the upper urinary tract may also be a factor when

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Read at annual meeting, South Central Section of American Urological Association, Colorado Springs, Colo October 18-20, 1954

[1] Ferris, D C and Odel, H M J A M A , 142: 634, 1950
[2] Boyce, W H and Vest, S A J Urol , 67: 169, 1952.
[3] Rosenberg, M L J Urol , 70: 569, 1953.
[4] Creevy, C D J Urol , 70: 196, 1953
[5] Boyce, W H J Urol , 65: 241, 1951
[6] Mitchell, A D and Valk, W L J Urol , 69: 82, 1953
[7] Ferris, D C and Odel, H M op cit
[8] Curry, F S and Bargen, J A Surg , Gynec & Obst , 60: 667, 1935
[9] Goldschmidt, S and Dayton, A B · Am J Physiol , 48: 419, 1919
[10] Bargen, J A J A M A , 132: 313, 1946
[11] Lapides, J Surg , Gynec & Obst , 93: 691, 1951
[12] Doroshow, H S J Urol , 70: 196, 1953
[13] Cordonnier, J J and Lage, W L J Urol , 66: 565, 1951.
[14] Bohne, A W J Urol , 70: 581, 1953

the urine is shunted into the intact large bowel from the bladder. The average intravesical pressure is 8 to 10 cm. of water, rising to 130 cm. at voiding, while the intrarectal pressure is 27 cm. of water rising to as much as 270 cm. of water on defecation.[15]

Boyce[5] and others have shown that the diversion of all the urinary stream into any part of the small bowel is incompatible with life. Animals that have had vesicocecostomy show reflux into the small bowel and die in from 15 to 24 days. On the other hand, electrolyte imbalance which developed in animals with vesicosigmoidostomy was promptly corrected when a proximal colostomy was established. The results of these animal experiments are highly significant when considered in the light of the other known facts about the physiology of the large bowel.

Chlorides and nitrogenous materials are absorbed from the intact colon, and the degree of absorption is directly proportional to the surface area of the involved bowel and the duration of contact with the urine. Absorption in the large bowel is probably most rapid from the cecum and diminishes progressively to little or no absorption from the rectum. If the large bowel is intact, it makes no difference how near the rectum the ureters are placed, because the urine will reflux back to the cecum. This is graphically demonstrated during a barium enema, although we, and others[11] have demonstrated it with urokon enemas. It is also frequently seen in patients who have had ureterosigmoidostomies into the intact bowel; intravenous pyelograms show the opaque material to be in the cecum as well as in the sigmoid and rectum.

From a historical standpoint it is interesting to review the anatomical possibilities which have been exhausted in the search for a suitable bladder substitute. These have already been adequately listed in the current literature.[16, 17] As far as those operations which presumably create an artificial sphincter, they had best not be listed or, as has already been written, "Only God can make a tree and the same is true of a sphincter."

The most marked advance in the technique of ureterointestinal anastomosis itself occurred with the revival of the "mucosa-to-mucosa" suture by Cordonnier.[18] The uniformly better anatomical results which followed this technique have almost put an end to "tunneling" type procedures. That acidosis developed later in these patients, even with good anatomical results as far as the upper urinary tract was concerned, soon became painfully evident. This factor more than anything else led to the search for a better substitute bladder than the intact large bowel.

Mitchell and Valk,[6] while recognizing the problem of acidosis, considered the technique of transplantation into the intact gut too valuable a procedure to be discarded. They have attempted, therefore, to handle the resulting acidosis by the following measures: 1) Transplant the ureters as low as is feasible in the rectosigmoid. (This measure is of questionable value because of the fluid reflux mentioned previously.) 2) Force fluids to 4500 or 5000 cc a day. 3) Give a low chloride diet. 4) Empty the rectum every 1 to 1½ hours. 5) Administer sodium bicarbonate 1 to 4 gm. a day. To this might well be added the use of a retention colon tube during the night connected to continuous drainage. By these measures acidosis may be controlled, but the ureters still empty into the fecal stream and bouts of pyelonephritis, progressive renal damage, and dilatation may be expected.

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[15] Kinman, L. M., Sauer, D., Houston, V. T. and Melick, W. F.: A. M. A. Arch. Surg., **66**: 531, 1953.

[16] Hinman, F. and Weyrauch, H. M.: Tr. Am. A. Genito-Urin. Surg., **29**: 15, 1946.

[17] Melick, W. F.: J. Urol., **62**: 454, 1949.

[18] Cordonnier, J. J.: Surg., Gynec. & Obst., **88**: 441, 1949.

Bricker[19] in his efforts to find a bladder substitute in cases of pelvic evisceration demanding removal of the bladder, rectum, and sigmoid, hit upon the idea of using isolated portions of the sigmoid colon. Finding many cases where this also had to be removed, he turned to the use of the isolated terminal ileum as a substitute bladder, as first suggested and carried out by Haffner. The comfort following this type of procedure is dependent upon a Rutzen bag to collect the urinary drainage. The electrolyte absorption following this type bladder substitution has been reported on by Eiseman and Bricker.[20] Urea passed freely from infusions into the isolated pouch. If hypertonic sodium chloride solutions were infused, an appreciable amount of chloride passed quickly into the bloodstream. Normally, however, chloride transfer was a slow process taking several hours to reach equilibrium. There was no detectable change in the blood chlorides in their human cases. The three factors of most importance are: 1) the concentration of the electrolyte; 2) the length of time the fluid remains in contact with the intestinal mucosa; and 3) the area of absorptive mucosa exposed. In human cases of pelvic evisceration the isolated ileal pouch with a separate colostomy for the fecal stream admirably solved the problem.

In the case of bladder carcinoma, where the rectum usually does not have to be sacrificed, it is possible to utilize the rectum and a very short piece of the sigmoid to construct a substitute bladder. Mauclaire[21] in 1895, and Kroenig[22] in 1907, suggested that if a fecal-free urinary reservoir could be provided with urinary control, infection, renal damage, and chronic acidosis might be minimized. Thus, we could hardly claim this as a new and original procedure. The single reference in the literature concerning possible difficulties was by Higgins who reported that he did permanent colostomies in dogs and found that the lower segment had contracted down to no capacity in 2 years.[23] One of us has already participated in a preliminary report and we have had no difficulty with the lower segment constricting down; on the contrary, we find that it becomes better adapted with the passage of time.[15]

A colostomy to divert the fecal stream has the marked advantage that infection, both immediate and late, is minimized. Thus, one has little or no fear of a urinary-fecal fistula in the postoperative period, and no difficulty with later pyelonephritis. The colostomy is an admitted disadvantage, requiring as it does, specialized care.[24] It is a well-established procedure, and in our minds, the advantages far outweigh the disadvantages. The problem of acidosis in our cases has been solved for the time being. It is well known, however, that some cases of ureterointestinal transplantation develop this unfortunate sequela years later so that the final answer is not yet at hand for any technique of bladder substitution.

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[19] Bricker, E. M.: S. Clin. North Amer., **30**: 1511, 1950.
[20] Eiseman, B. and Bricker, E. M.: Ann. Surg., **136**: 761, 1952.
[21] Mauclaire [illegible] . 546, 1900, cited by Papin, 1925.
[22] Kroenig: [illegible] 1907.
[23] Higgins, [illegible] **60**: 874, 1948.
[24] Lyons, A. S., Robinson, B., Schreiber, G. and Turell, R.: Modern Medicine, February 15, 1954.

Theoretically one may calculate the expected risks. All patients who have had any type of ureterointestinal transplantation must force fluids; this in turn reduces the concentration of excreted chlorides. Since the concentration of chloride within the lumen of the gut seems to be of primary importance in determining its absorption, this may be the most important prophylactic measure. It is also of value to use just as little of the sigmoid as possible, since the distal portions of the large bowel are the least absorptive. This is an important point for if the patient is to be comfortable, he should be able to contain the urine for 2 or 3 hours during the day and 3 or 4 hours during the night. This admittedly increases the time for possible absorption, but it does expose a less absorptive mucosa than the ileum or cecum. The alternate procedure would be to use the ileal segment for the collection of urine and re-establish the fecal stream. The Rutzen bag has been shown to provide comfort for these patients as far as urinary drainage is concerned. Here one uses a more absorptive portion of the gut, but since the drainage is continuous, the length of time that the urine is in actual contact with the gut mucosa is reduced. It would seem reasonable to us that if a bag type urinary collection system is to be used anyway, that it would be far easier to use cutaneous ureterostomies with the Rutzen bag. Technically it is easier and quicker to construct a rectosigmoidal pouch and do a colostomy than it is to make an ileal pouch and do a ileoileostomy.

From the esthetic point of view, one might question whether it is better to have a colostomy with urinary control, or fecal control with a Rutzen bag constantly collecting urine. Both groups of patients have to make adjustments and concessions to their altered physiology and many in each group have done so and returned to society and their jobs. At the present time we have several patients who have the ileal pouch, but we have been unable to judge whether or not their adjustment has been any different from those with a colostomy. Time and a critical evaluation of all procedures will alone tell the story.

TECHNIQUE

Preoperatively it is important to do a careful rectal examination to be certain that the rectal sphincter tone is entirely normal. For preoperative preparation of the bowel we have used sulfasuxidine and aureomycin, but recent work would indicate that neomycin and phthalylsulfathiazole might be preferable. Sterile water enemas are given the morning of surgery until the returns are clear. A midline incision is made from the symphysis around the umbilicus. If exploration shows no evidence of metastases the bladder dissection is done first. In the male we have found it of advantage to first approach the prostate as would be done in a radical retropubic prostatectomy. After the prostate has been freed and the urethra severed it is possible to completely free the base of the bladder back to the peritoneum. The entire peritoneal floor is then freed, and it is now possible to dissect out the lateral vascular bladder network on either side working from above down to the previously free base. The ureters are cut from the bladder on either side and allowed to remain in the wound. In the female it is possible to remove the tubes, ovaries, broad ligaments and uterus along with the bladder in one block. After the bladder has been removed the sigmoid is measured with the remaining ureters and at a convenient level is doubly clamped and divided. The distal end is then closed with an inverting suture and the suture line reinforced with interrupted mattress sutures of fine silk. Just proximal to the cut end of the ureter a fine silk suture is placed through the adventitia and through the muscularis of the sigmoid and tied. This holds the ureter in position. A very small stab wound is made into the lumen of the sigmoid and the mucosa carefully identified. Four sutures of fine chromic gut are then placed through the entire ureteral wall and the mucosa of the sigmoid so that the knots are on the outside and tied. If there is any marked urinary leakage, a second row of sutures may be taken through the muscularis of the sigmoid and the adventitia of the ureter. The same procedure is carried out on the other side. We believe that it is better to do the anastomosis last because if it is done first, the anastomosis may be damaged by the manipulations during the cystectomy. The clamped, proximal end of the sigmoid is brought out to the skin, the mesocolon sutured laterally to prevent possible herniation and postoperative intestinal obstruction. No attempt is made to close the posterior peritoneum. The wound is drained and closure is by interrupted wire sutures with silk for the skin. Postoperatively a rectal tube is allowed to drain continuously for three or four days. Likewise, a continuous gastric suction is maintained through a nasal tube until definite peristalsis returns to the intestines. The colostomy may be released any time after 18 hours

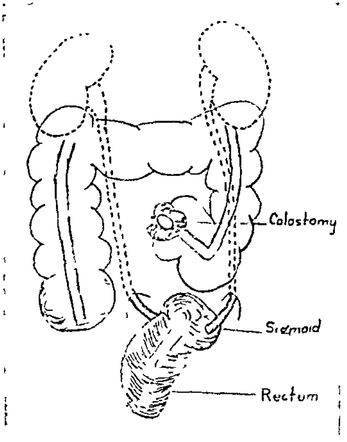

FIG. 1. Diagrammatic picture of completed ureteral transplantation into rectosigmoidal pouch and proximal colostomy.

but preferably after 72 hours. For the first few weeks after the removal of the rectal tube the patient usually experiences frequency, urgency and nocturia, but in our cases thus far, these have disappeared and the patient is able to hold the urine from three to four hours without difficulty. The patient is taught proper care of his colostomy and how to irrigate it as soon as he is ambulatory. A diagrammatic view of the completed procedure is shown in figure 1.

CASE REPORTS

Case 1. L. S., a 67-year-old woman, was seen on March 31, 1952 complaining of hematuria of 8 years' duration. Cystoscopy showed a fungating lesion involving the floor of the bladder, the external sphincter, and the urethra. Vaginal examination disclosed that the tumor had eroded through the urethra into the anterior vaginal wall, and from the base of the bladder the tumor apparently extended into the parametrium. An excretory urogram (fig. 2) showed a nonfunctioning left kidney and right hydronephrosis. On April 7, 1952 the uterus, broad ligaments, ovaries and bladder were dissected *en bloc* from above, and with a cautery, the urethra, upper two-thirds of the vagina, and the cervix were freed from below and the entire mass removed. The ureters were then implanted into a rectosigmoidal pouch and a colostomy done. The pathology report showed carcinoma of the bladder, grade 4, with extension into the urethra and vagina. Locally, the tumor had deeply invaded the muscularis of the bladder, but was not completely through the wall. The patient to date has shown no evidence of recurrence, acidosis, or urinary infection. Excretory urograms made 10 days, 2 months, and 1½ years postoperatively are shown in figure 2.

Case 2. R. S., a 46-year-old man, was first seen on March 15, 1952 because of severe hematuria. He was also a severe diabetic and had recently been discharged with arrested pulmonary tuberculosis. Cystoscopy showed an infiltrated appearing tumor over and around the left ureteral orifice. Because of his poor general condition transurethral resection of the tumor was carried out. On June 21, cystoscopy showed a massive recurrence and excretory urograms showed marked left hydronephrosis. On July 8 the ureters were transplanted to a rectosigmoidal pouch; a colostomy and cystectomy were performed. The patient made an uneventful recovery with no change in the serum electrolytes. Excretory urograms made 4 months postoperatively showed a complete return of the kidneys to normal and are compared with the preoperative urogram in figure 3. The pathologist reported that the tumor was carcinoma, grades 3 to 4. Approximately 8 months later the pulmonary tuberculosis again became active and the patient was admitted to a sanatorium where he died of pulmonary hemorrhage.

Case 3. B. G., a 58-year-old white man, was admitted to the hospital for proposed cataract surgery. He denied any urinary complaints but was referred for urological investigation because the admission urinalysis showed microscopic hematuria. Cystoscopy revealed an extensive carcinoma involving most of the bladder. A biopsy obtained under general anesthesia revealed a grade 1, transitional cell carcinoma. Bimanual examination under anesthesia showed no evidence of fixation. Excretory urograms made January 1, 1954 showed right

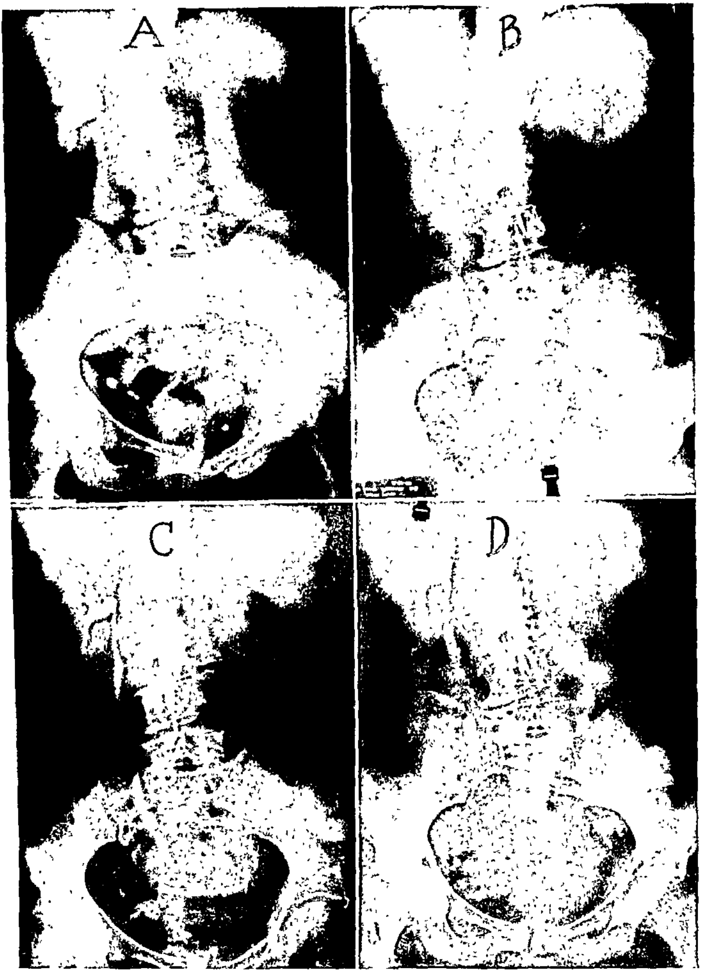

FIG. 2. Case 1. *A*, preoperative 25 minute excretory urogram; nonfunctioning left kidney and right hydronephrosis. *B*, 15 minute pyelogram 10 days postoperatively. *C*, 5 minute urogram 2 months postoperatively; complete disappearance of hydronephrosis. *D*, 15 minute urogram, 1½ years postoperatively; right kidney remains normal; no evidence of function on left.

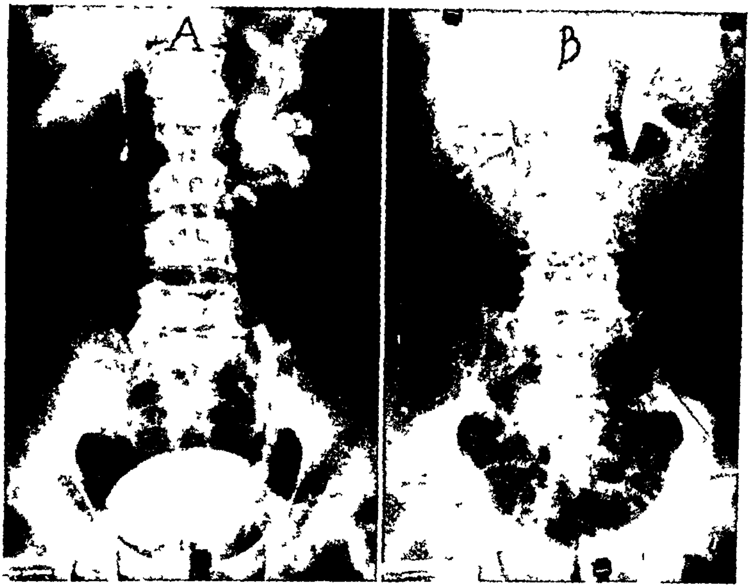

FIG. 3 Case 2 A, preoperative 1½ hour excretory urogram; marked left hydronephrosis. *B*, 20 minute urogram 4 months after transplantation; note return of upper urinary tract to normal.

hydronephrosis with a blocked left kidney as evidenced by a nephrogram. Cystectomy, transplantation of the ureters to a rectosigmoidal pouch, and colostomy were done January 8. Pathological examination of the surgical specimen revealed the same grade tumor as the biopsy, but the tumor had infiltrated through the muscularis of the bladder over the right ureteral orifice. The patient had an uneventful postoperative course and the electrolytes remained normal. Excretory urograms made 12 days and 6 months postoperatively showed a return of the kidneys to normal and are compared with the preoperative findings in figure 4. Recently, however, the patient was readmitted because of a large right flank mass. This was drained and deep x-ray therapy given, but the patient died. Autopsy disclosed a massive retroperitoneal metastatic lesion. Blood chemistry and excretory urograms remained normal up to the time of death.

Case 4. J. A., a 59-year-old man, was referred to us because of a "bladder tumor," found elsewhere on observation cystoscopy. The past history, however, revealed that 4 years ago the patient had been informed that he had a "cancer of the prostate gland" and had taken female hormones for several years. The present complaints were limited to burning, frequency, and nocturia. Rectal examination revealed a small, hard prostate that was not fixed. Excretory urograms showed a nonfunctioning right kidney with moderate hydronephrosis on the left. Observation cystoscopy showed a tumor mass extending from the prostate up around the right ureteral orifice. Biopsy of this tumor and a needle biopsy of the prostate showed prostatic carcinoma. Metastatic x-ray series failed to reveal any evidence of metastases and the alkaline and acid serum phosphatase levels were normal. The prostate, seminal vesicles and bladder were removed, the ureters transplanted into a rectosigmoidal pouch, and a colostomy done. The patient made an uneventful recovery and the electrolytes remained

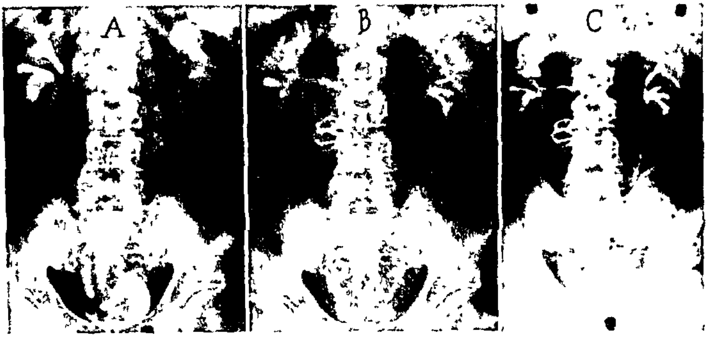

FIG. 1. Case 3. *A*, preoperative 25 minute excretory urogram; note right hydronephrosis and blocked left kidney, as evidenced by left nephrogram. *B*, 5 minute urogram 12 days postoperatively; note return of kidneys to normal. *C*, 6 months postoperatively; normal excretory urogram.

normal. Before discharge from the hospital the patient had a sudden attack of severe headache and marked hyperpyrexia and lapsed into coma; he expired without regaining consciousness in about 8 hours. While permission for an autopsy could not be obtained, we believe that the death was due to a cerebral vascular accident.

Case 5. J. U., a 69-year-old woman, was admitted to the hospital in shock because of sudden hemorrhage from the bladder. Blood transfusions were immediately started, and when the blood pressure rose, she was taken to the cystoscopic room where about 1500 cc of blood and clots were evacuated. Observation cystoscopy showed multiple tumors over the entire bladder, involving the external sphincter and posterior urethra. Excretory urograms were normal. On May 21, 1953 the ureters were transplanted to a rectosigmoidal pouch, a colostomy done and the bladder, urethra, and anterior two-thirds of the vaginal wall resected along with the tubes, ovaries, broad ligaments and uterus. The patient had an uneventful postoperative course except for quite a period of depression over her altered physiology. However, as she became more familiar with the care of the colostomy and regained confidence, she adjusted well, returned to her former work and has been working ever since. The serum electrolytes have remained entirely normal. Excretory urograms made 1 month and 6 months postoperatively show a normal upper urinary tract and are compared with the preoperative findings in figure 5.

Case 6. E. L., a 70-year-old man, was admitted to the hospital on July 23, 1951 complaining of terminal hematuria of 3 months' duration. Excretory urograms showed some reduction of renal function due to old bilateral chronic pyelonephritis. Cystoscopy revealed a papillary growth on the left lateral wall extending from the dome of the bladder to the floor. A biopsy was reported as a papillary carcinoma, grade 1, with no infiltration into the musculature. A suprapubic cystotomy was done and the tumor removed with a cautery and the base fulgurated. The pathological report of the surgical specimen was consistent with

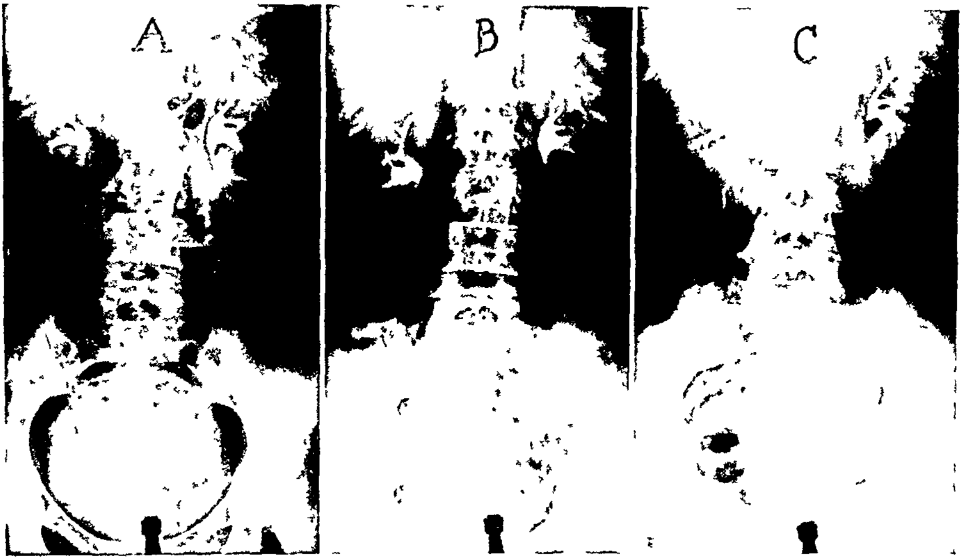

FIG. 5. Case 5. *A*, preoperative 10 minute excretory urograms are normal *B*, 10 minute excretory urograms remain normal 1 month postoperatively. *C*, 10 minute excretory urograms remain normal at 6 months postoperatively.

the biopsy report. The patient returned 3 months later for followup and observation cystoscopy showed no recurrence. He was not seen again until April 8, 1952 at which time cystoscopy showed multiple papillomas, with the same biopsy findings. Due to the multiplicity of the lesions, complete cystectomy, transplantation of the ureters to a rectosigmoidal pouch and colostomy were done by Dr. Lindell M. Kinman. The surgical specimen showed limited invasion of the bladder muscularis. Excretory urograms made 1 month, 1½ years, and 2 years postoperatively are about the same functionally and anatomically as the preoperative picture and are shown for comparison in figures 6 and 7. During the postoperative period the chlorides began to be mildly elevated, ranging from

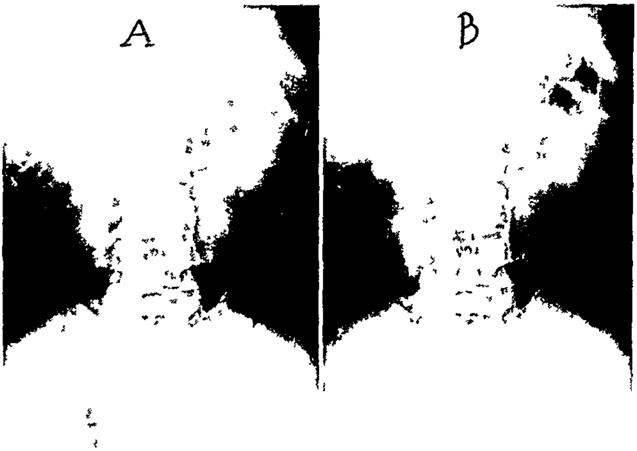

FIG. 6. Case 6 *A*, preoperative 5 minute excretory urogram; note poor function and contracted kidneys, interpreted as probably due to chronic pyelonephritis *B*, preoperative 15 minute excretory urogram; note poor renal function and somewhat contracted kidneys.

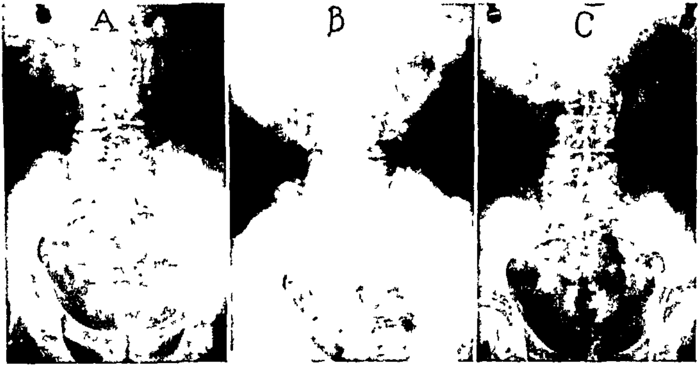

Fig. 7 Case 6. Five minute excretory urograms *A*, 1 month postoperatively. *B*, 6 months postoperatively *C*, 2 years postoperatively

110 to 113 m/Eq. and the CO_2 combining power ranging from 20.7 to 12.6 m/Eq. He was placed on 40 to 60 gr. of sodium bicarbonate daily. Over the next 1½ years the patient was admitted to the hospital on several occasions in acidosis, which was readily corrected by intravenous lactate solution.

On March 16, 1954 the patient was re-admitted because of clinical signs of acidosis. The chlorides were 119 m/Eq. and the CO_2 combining power was 15.3 m/Eq On intravenous lactate he responded well and was maintained on an oral dose of 160 gr. of sodium bicarbonate daily. It occurred to us that some study of the rectosigmoidal pouch might throw some light on the cause of the acidosis. A previous x-ray had been obtained after the operation by instilling an opaque

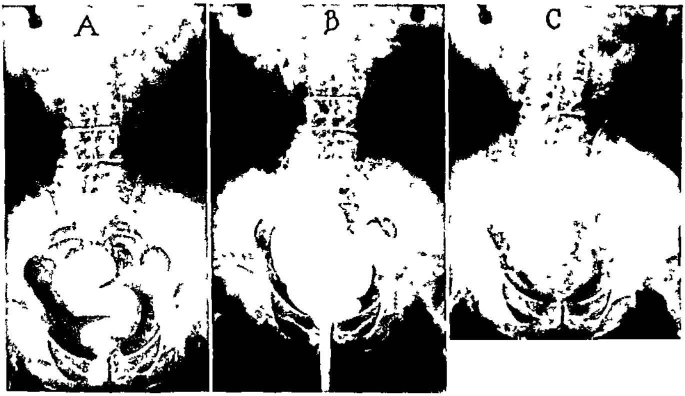

Fig 8 Case 6 *A*, x-ray appearance of rectosigmoidal pouch shortly after surgery *B*, 2 years postoperatively, note dilatation *C*, film taken after voiding shows considerable retention in pouch.

enema (fig. 8, *A*). The pouch was again filled to mild pressure with diluted 70 per cent urokon and an x-ray obtained. The patient then voided and the second x-ray disclosed considerable retention (fig. 8, *B* and *C*). There are three possible causes for the acidosis: 1) The sigmoidal loop has become quite long and dilated, offering a large surface area for absorption. 2) Incomplete emptying allows stasis and an increased time of exposure of the urine to the intestinal mucosa. 3) The patient had chronic bilateral pyelonephritis which has continued its progression. We then checked the other patients in this series who have had no acidosis and found that they did not have any rectal retention after voiding.

SUMMARY

The use of the rectosigmoidal pouch as a substitute bladder in this limited series has had the following advantages:

Urinary continence is preserved by utilizing the rectal sphincter.

Urinary obstruction and infection are eliminated by the diversion of the fecal stream.

The danger of fecal fistula has been eliminated.

Technically the surgery is easier than in other described "surgical artificial bladders" and more quickly performed which should result in a lower operative mortality.

Hyperchloremic acidosis has been no problem except in the one case cited where there was a pre-existing chronic pyelonephritis and where there is incomplete emptying of the rectosigmoid.

The only disadvantage is that the patient does have a colostomy which requires specialized daily care. Whether this is less desirable from an esthetic point of view than control of the fecal stream with a constantly draining urinary sinus is, in our minds at least, still unsolved.

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FURTHER OBSERVATIONS ON VESICOURETERAL REFLUX

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In a previous paper observations were presented on vesicoureteral reflux of 56 patients with spinal cord injuries. This article dealt also with the pertinent literature available at the time of writing. Additional studies have since then appeared, which dealt with cause and treatment of reflux. The present study tries to analyze observations made on 144 patients with reflux encountered among 1083 patients, 97 of whom did not have traumatic spinal cord lesions and who were seen over an 8½-year period at this paraplegia center. One group of these patients merits closest scrutiny: those who had neurosurgical interventions such as anterior or posterior rhizotomies, chordotomies, pudendal or sacral neurotomies and injection of absolute alcohol into the subarachnoid space. Another group was treated with straight drainage in order to evaluate its effect on reflux.

MATERIAL AND METHOD

One hundred thirty-six patients had injuries to the spinal cord and/or cauda equina. Eight patients were paralyzed from nontraumatic causes. One hundred and one had upper motor neuron lesions and 43 had lower motor neuron lesions in regard to the activity of the pelvic floor (conus). Table 1 reflects the distribution regarding the level of the lesion. The ratio of reflux in regard to upper and lower motor neuron lesions, caused by trauma, was 93:43; and it was 101:43 if also the nontraumatic group was included.

A 30 minute delayed cystogram was performed in those cases in which reflux was not demonstrated immediately on the first film. This method was thought sufficient for this investigation in contradistinction to cystographic cystometry presented in the previous study. Although the latter method is more accurate it is also more time-consuming and less economical.

According to the most frequently observed anatomical landmarks at which reflux could be seen, a classification was devised which consisted of reflux at 1) posterior inferior iliac spine, 2) posterior superior iliac spine, and 3) pyelogram.

OBSERVATIONS

Table 2 presents an evaluation of the ratio of reflux pyelogram in respect to laterality. It seems that a reflux pyelogram is significantly more frequent on the right than on the left where complete lesions are concerned, whereas no marked difference was seen in patients with incomplete lesions.

Table 3 presents the overall laterality of reflux which again reflects the higher incidence on the right.

Table 4 shows the incidence of reflux of patients whose upper motor neuron

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TABLE 1. *Distribution of upper and lower motor neuron lesions related to level of lesion*

	UMNL	LMNL
Cervical complete	8	2
Cervical inc.	12	2
Thoracic 1–6 comp.	19	3
Thoracic 1–6 inc.	5	0
Thoracic 7–12 comp.	38	13
Thoracic 7–12 inc.	8	2
Lumbar complete	2	7
Lumbar incomplete	1	14
Tum. or dis.	8	0
	101	43

TABLE 2. *Relation of reflux to level of lesion*

	Right	Left
Tumor or disease	6	3 (P* 2:1)
Complete lesions	80	49 (P 52:33)
C	8	4 (P 6:2)
T 1–6	20	13 (P 14:8)
T 7–12	45	27 (P 28:18)
L	7	5 (P 4:5)
Incomp. lesions	33	27 (P 20:15)
C	11	9 (P 6:7)
T 1–6	3	5 (P 3:4)
T 7–12	7	6 (P 4:3)
L	12	7 (P 7:1)

* Pyelogram

TABLE 3. *Laterality of reflux*

No. of patients			144
No. of ureters			288
	Right	*Left*	
*PIIS	37	23	60
*PSIS	7	7	14
*L4–5	1	0	1
*P	74	49	123
None	25	65	90

*PIIS = post inf. iliac spine.
*PSIS = post sup. iliac spine.
*L4–5 = between lumbar vertebra 4 and 5.
*P = Pyelogram

lesions were artificially converted into lower motor neuron lesions by means of a subarachnoid injection of alcohol or sacral extradural neurotomy.

Sixty-four patients received alcohol injections because of skeletal spasticity or autonomic hyperreflexia from distention of hollow viscera (manifested by par-

TABLE 4 A, *subarachnoid alcohol block and reflux B, sacral neurotomy and reflux*

A	
No of alcohol blocks	77
No of patients	64
No of patients without reflux before or after	46
No of patients with reflux before or after	18
B	
No of patients with sacral neurotomy	9
No of patients without reflux before or after	6
No of patients with reflux before or after	3

oxysmal hypertension, excessive diaphoresis, headache, etc.) Forty-six patients had no reflux before or after the block. Eighteen patients had reflux at some time before or after the block, among these, ten ended up without reflux while seven had reflux and one died of uremia without reflux studies. It should be noted that among those 7 patients who had eventually reflux, improvement was observed in two and that reflux was inconstant in that it was absent in some cases for a long period (28 and 19 months after block), yet was present after additional 41 and 39 months respectively.

Nine patients underwent sacral neurotomy, eight because of paroxysmal hypertension and one because of bladder dysfunction, 3 patients had reflux at one time or other preoperatively, one of these retained reflux postoperatively and in the remaining 2 cases reflux could not be demonstrated postoperatively.

Table 5 shows the relationship of reflux and pudendal neurotomy or neurotripsy which was done on 32 patients. Eight had reflux at some time before or after the intervention with the following distributions: five had reflux before operation, one had no reflux preoperatively, showed reflux after unilateral operation (PHS right), but had none at last examination 16 months following the bilateral procedure, 2 patients had no reflux preoperatively but showed it postoperatively. Four of the 5 patients with preoperative reflux retained it postoperatively.

Table 6 shows reflux and chordotomy. Only 3 patients had reflux before or after chordotomy, in one of whom reflux developed 28 months postoperatively and the remaining 2 patients retained their reflux which was present preoperatively.

TABLE 5 *Pudendal neurotomy or neurotripsy and reflux*

No of pudendal operations	55
No of patients	32
No of patients without reflux before or after	24
No of patients with reflux before or after	8

TABLE 6 *Spinothalamic tractotomy and reflux*

No of patients with chordotomy	27
No of patients without reflux before or after	24
No of patients with reflux before or after	3

TABLE 7. *A, posterior rhizotomy and reflux. B, Anterior rhizotomy and reflux*

A.	
No. of patients with post. rhizotomy	8
No. of patients without reflux before or after	6
No. of patients with reflux before or after	2
B.	
No. of patients with ant. rhizotomy	10
No. of patients without reflux before or after	8
No. of patients with reflux before or after	2

TABLE 8 *Effect of straight drainage on reflux*

No. of patients	31
No. of patients with disappearance of reflux with continuous straight drainage	13
No. of patients with disappearance of reflux with previously balanced bladder	11
No. of patients with disappearance of reflux with suprapubic catheter	1
No. of patients with disappearance of reflux with intraureth. cath.	1
No. of patients with disappearance of reflux despite removal of straight drainage	3
No. of patients with improvement of reflux	10
No. of patients without improvement on suprapubic drainage	5
No of patients without improvement on intraurethral drainage	3

Table 7, *A* shows posterior rhizotomy and reflux. This operation was done in order to control autonomic hyperreflexia. The 2 patients with reflux had it preoperatively; one of them did not show 37 months postoperatively. The other continued to have reflux. In contrast 6 patients displayed no reflux either pre- or postoperatively.

Table 7, *B* shows anterior rhizotomy and reflux. Anterior rhizotomy was done in order to control skeletal spasticity. Here again were two out of 10 patients who had reflux prior to intervention. One of them showed no reflux postoperatively while the reflux condition of the other remained undetermined.

Table 8 shows the therapeutic effect of straight drainage on reflux. A total of 31 patients were subjected to this treatment. Twenty-three patients benefited from this treatment among whom thirteen had a complete disappearance and 10 had improvement of reflux according to the previously described anatomical landmarks. Of the 13 patients whose reflux disappeared, eleven had well balanced bladders. The other 2 patients had an intraurethral and a suprapubic catheter respectively at the time of discovery of reflux. Eight patients had no improvement, five of whom had suprapubic and three intraurethral drainage since injury.

DISCUSSION

This study shows that the incidence of reflux among paraplegic patients was 144 out of 1083 or 13.3 per cent. This figure is lower than the figures quoted in our previous article and may be of greater statistical value because a total of only 238 cases were screened in our first communication. Yet, this optimism must be duly dampened by the fact that not all of the 1083 patients had routine screening since leaving the hospital so that some of them may have an undetected

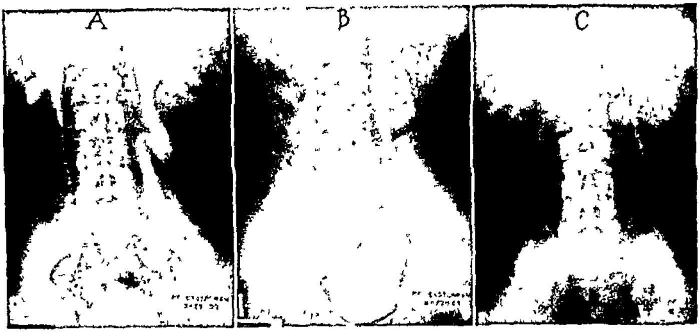

FIG. 1. *A*, cystogram of patient with complete cord lesion at D1. Bladder function well balanced following transurethral resection and subarachnoid alcohol block. *B*, cystogram of same patient after treatment with straight intraurethral drainage for 39 months. *C*, excretory urogram of same patient after treatment with drainage for 11 months.

reflux. The previous findings, namely, that reflux occurs more frequently in patients with upper than with lower motor neuron lesions is confirmed. However, the ratio has changed somewhat. While it was 75 per cent:25 per cent in our first study it is 70 per cent:30 per cent in the present investigation. This should be taken as a warning against converting, intentionally and for presumably therapeutic reasons, upper into lower motor neuron lesions because of the above presented evidence that reflux can very well occur with well functioning lower motor neuron bladders (fig. 1, *A*).

Why reflux occurs more frequently on the right than on the left (ratio of 119:79) remains an open question. In this connection it was also observed that the incidence of morbidity and nephrectomy was higher on the right than on the left although the respective nephropathy could not be traced directly to reflux.

A reflux pyelogram was present in 123 of a total of 198 refluxes. Seventy-five refluxes had not reached the pyelogram stage. In these cases reflux extended in 60 instances up to the posterior inferior iliac spine, in 14 instances up to the posterior superior iliac spine and in 1 instance to the level between the fourth and fifth lumbar vertebrae or, in other words, up to the line between the middle and the lower third of the ureter. Satani has shown that longitudinal fibers are dominant in the lower third of the ureter and that circular fibers form but a broken circle. It appears as if reflux is prevented from further extension toward the kidney by the intact circular fibers of the middle third of the ureter. Whether neurogenic factors play a role in addition to these known myogenic facts will have to await further study.

Reflux in connection with subarachnoid alcohol block was seen in only 12.5 per cent of 64 patients while 56 patients remained so far without it. This does not imply that they may not develop reflux at a later date, although the observation time was many years in some instances. The reflux of the 12.5 per cent may or may not have had a causal relation to the block. The clinical neurologic deficit from alcohol block is similar to that after a combined anterior and posterior rhizotomy following which a 56 per cent improvement of reflux was reported. Our experience with alcohol blocks has not shown similar results. However, no observation time was mentioned by Brendler et al. and the end result must be viewed with caution because of the following long range observation: 2 cases who had no reflux 28 and 49 months respectively after block showed it after an additional 41 and 39 months respectively.

Following sacral neurotomy two of our 3 cases with reflux showed none postoperatively and are too few to permit judgment inasmuch as the observation time was too short.

Eighty per cent of the patients with pudendal neurotomies or neurotripsies demonstrated no reflux but 20 per cent did. Of these 15 per cent had reflux preoperatively. Only in 2 cases did reflux disappear eventually following pudendal nerve operation. However, the series is much too small to permit any conclusions.

As was to be expected, no relationship could be established between chordotomy and reflux. If reflux be caused in some instances by changes in the proprioceptive pathways of the bladder this condition will not change after chordotomy because the proprioceptive fibers from the bladder travel in the posterior columns which are not affected by an anterolateral spinothalamic tractotomy.

Only in 1 case was disappearance of reflux observed following posterior rhizotomy, done to treat autonomic hyperreflexia. In another case reflux persisted following this operation which admittedly interrupts postural impulses from the bladder. The same condition, namely, disappearance or persistence respectively, of reflux was seen in 2 patients with anterior rhizotomy. Inasmuch as anterior rhizotomy, if done for skeletal spasticity, intentionally spares the sacral outflow in order not to interfere with bladder function no reflux changes on that basis can be expected.

Clinical improvement, i.e., disappearance of bouts of chills and fever, occurred so far in all of our patients with straight catheter drainage, in excess to the 31 patients presented here with accurately controlled observations. It is interesting that among the patients whose reflux persisted despite straight drainage, five had suprapubic and three intraurethral catheters. This corroborates previous findings of Talbot and Bunts. On the other hand, there were only 2 patients with disappearance of reflux despite suprapubic or intraurethral drainage. Comparison of these two groups shows that reversibility depends most likely on absent anatomical changes. Further evaluation showed that completeness of the lesion plays no role regarding disappearance of reflux because eight of the 13 patients with disappearance of reflux had complete and three incomplete lesions. The observation time ranged from 1 to 77 months. Another interesting fact is that a well balanced bladder is no guarantee against the appearance of reflux because 11 of the 13 patients with complete disappearance of reflux had well balanced bladder function prior to the discovery of reflux. Although the goal of bladder rehabilitation remains unchanged and was achieved by us in 74 per cent of 844 patients, namely, to remove eventually the catheters, close attention should be paid to the kidney condition which is vital for the patient rather than the best bladder function *per se*. In confirmation of the findings of Hutch and Bunts kidney function of our patients also shows a tendency to decline in later years of paraplegia for which in some instances, reflux may be responsible.

The question remains as to when and how to treat vesicoureteral reflux. We concur fully with Talbot's view that this condition requires treatment only when it causes clinical manifestations, such as chills and fever, or when it leads to radiologically demonstrable impairment of kidney function.

Correction of reflux has been observed following two ways of approach: one urological, the other neurosurgical. The urological approach is one of three procedures: Hutch's operation, cutaneous ureterostomy or straight bladder drainage (fig. 1, *B* and *C*). Hutch's intervention, successful in his hands, has not yet been done routinely in paraplegia centers because of the difficult indication in respect to timing. In those cases of reflux, with obstructive ureteral kinks and hydronephrosis, in which straight drainage brings no improvement within 3 months, ureterolysis and cutaneous ureterostomy with or without cuff is the method of choice although in some instance even a nephrostomy may become necessary. We apply straight bladder drainage earlier than others, even in the absence of clinical manifestations (chills and fever), at the moment when the pyelogram shows marked progression of pyelonephritis. Pyelonephritis and the reflux may yet respond to early treatment.

Changes and improvement of reflux have been reported, including our own experience presented above, following various neurosurgical procedures, such as anterior and posterior rhizotomy, sacral neurotomy and conectomy. These observations prove that neurogenic factors may also be responsible in the etiology of reflux, as postulated earlier. However, it is nay impossible to estimate, prognosticate and therefore indicate whether and, if at all, at what time any of these various procedures will be beneficial in the respective case. The neuroanatomy and neurophysiology of the ureter is still a controversial issue. While some deny all influence of extrinsic nerves on ureteral activity and believe that ureteral nerves are only sensory and vasomotor, others leave the question of nervous impulses on ureteral peristalsis open, and still others believe that extrinsic neurogenic impulses are also important in addition to the myogenic autonomous propulsion of urine. Until more specific knowledge is provided regarding the normal neuroanatomy (other than intrinsic ganglia of the ureter) and the neurophysiology of the various segments of the ureter, a rational neurosurgical approach lacks scientific justification. Until such time the urological treatment will be preferable.

On the other hand, our evidence, reported here, shows that neurosurgical interventions will not be detrimental urologically as long as the indication is based upon the respective condition which requires neurosurgical correction (spasticity, autonomic hyperreflexia, pain) and as long as vesicoureteral reflux *per se* is not the indication to perform neurosurgery.

SUMMARY

One hundred forty-four patients with reflux were examined out of a total of 1083 patients, an incidence of 13.3 per cent.

The ratio of reflux in upper motor neuron lesions to lower motor lesions was 70 per cent to 30 per cent.

Reflux appeared more frequently on the right than on the left (119:79). Pyelograms resulted from reflux in 123 patients while in seventy-five reflux stopped at the border between middle and lower third of the ureter, indicating that the circular muscle fibers of the middle third of the ureter were an effective barrier.

Sixty-four patients had subarachnoid alcohol blocks; 8 patients had sacral neurotomies; 32 patients underwent pudendal nerve operations; 27 patients had spinothalamic tractotomies (chordotomies); 10 patients had anterior rhizotomies; 8 patients had posterior rhizotomies. None of these neurosurgical interventions disclosed a causal relationship to reflux; therefore, neurosurgical operations can be performed without urological detriment. The above described neurosurgical procedures should be used to correct the respective neurologic condition rather than vesicoureteral reflux.

Vesicoureteral reflux of 31 patients benefited from straight drainage which remains the method of choice until vesicoureteral reflux will be understood on a neuroanatomical and neurophysiological basis. A well balanced bladder function does not prevent reflux.

Straight bladder drainage becomes indicated when reflux is associated with chills and fever and/or progressive renal damage, even in the presence of good bladder function.

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SURGERY ON THE EXSTROPHIED BLADDER: PRELIMINARY REPORT

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Achievement of a satisfactory result in treatment of exstrophy of the bladder is one of the most difficult surgical problems in urology.

The procedures most often employed are urinary diversion and extirpation of the defective bladder, with attempt to correct the abdominal and genital defects by plastic repair. Some type of ureterosigmoidostomy is the common method of urinary diversion. The immediate mortality rate for this procedure is not high and the clinical course—for the most part—is fairly satisfactory for a considerable period. However, the overall clinical picture later on plus physiologic data pertaining to urinary diversion, as recently derived from detailed laboratory research, suggest that the presently accepted surgical approaches fall far short of a satisfactory solution of exstrophy of the bladder.

An improved means of treating this anomaly would seem long overdue. Among the newer contributions to methods of plastic repair and to knowledge of the healing of wounds are many principles and procedures that may well be applicable to management of exstrophy of the bladder. Moreover, many of the individual problems inherent to some aspects and complications of exstrophy are identical to problems presented by unrelated lesions for which surgical solutions have been determined.

With these considerations in mind I am currently investigating various procedures in the hope of effecting satisfactory repair of this congenital deformity.

Because ureterosigmoidostomy has been, in the past, the procedure most commonly utilized, a brief reference to its undesirable features is pertinent to this discussion. Predominating hazards are electrolyte imbalance, infection, and obstruction. Numerous reports on these factors by competent investigators are now available and point to the strong probability that electrolyte derangement will develop in patients who have undergone ureterosigmoidostomy. Repeated blood studies at various intervals reveal that approximately 80 per cent of such patients have hypokalemia, 100 per cent hyperchloremia, 75 to 80 per cent reduction of alkaline reserve, and 35 to 40 per cent hyponatremia.

Infection plays a much larger role in the over-all late results than usually is appreciated. It is estimated that a considerable degree of infection, often not manifest clinically, ultimately develops in most of the patients. Reflux of the bowel content into the transplanted ureters is a common finding. Although pyelographic information often is inadequate due to reliance almost solely upon excretory urograms, correlation of these data with subsequent observations at autopsy indicate that hydronephrosis and pyelonephritis may occur despite the absence of obstruction. From my own observations I believe the nephritic factor of pyelonephritis is of dominating significance. Some degree of obstruc-

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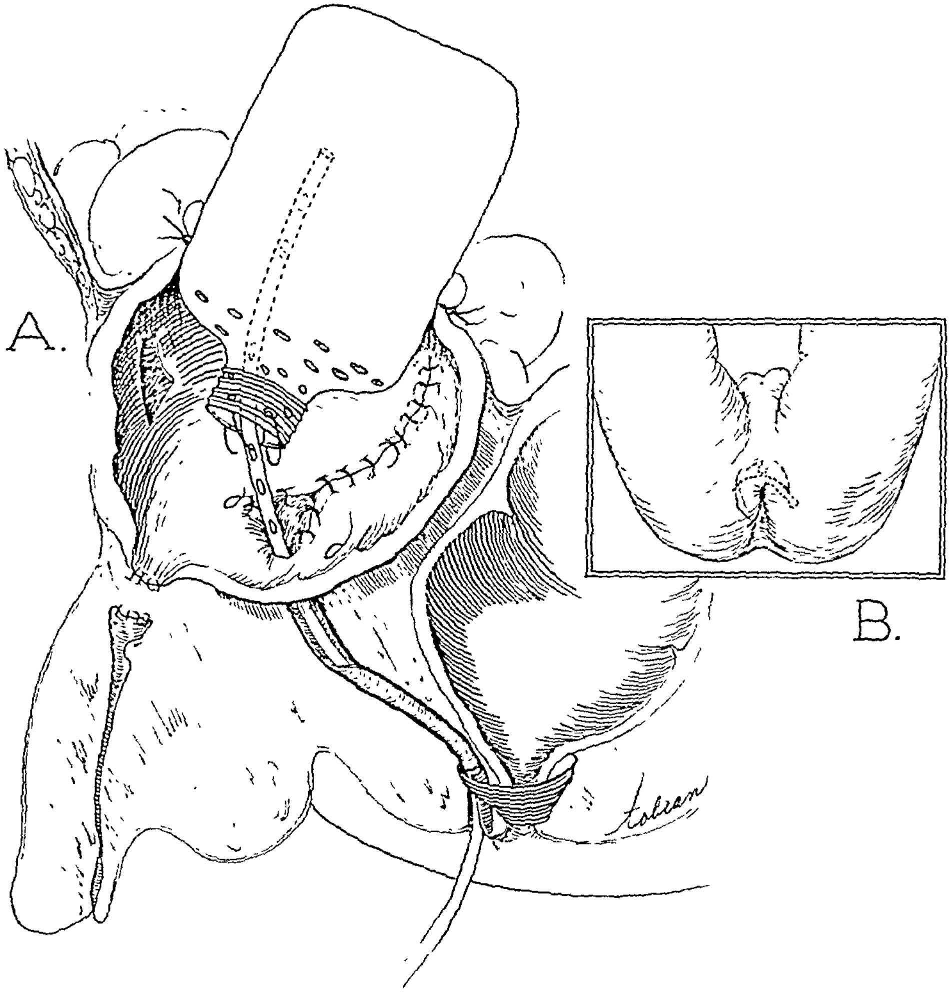

FIG. 1. *A*, new vesical neck in the dependent portion of the bladder, together with new urethra extending under rectal sphincter. Retention catheter extends into polyethylene container that is used as mold, permitting regrowth of bladder around it, increasing vesical capacity. *B*, perineal flap of skin which is extended back under rectal sphincter to be subsequently joined by mucosal flap extended down from bladder.

not have perfect continence. If only a small amount of urine is present in the bladder it can be retained, but with larger quantities, dribbling occurs not only through the urethra but also through a small fistula presenting at the site of the abdominal closure. The plastic repair has a good appearance and a suitable urinary reservoir has been effected. It is hoped that the child will develop better continence. If not, after a suitable trial period, we have other surgical measures in mind that may be of help. These will be discussed later in this report.

Exstrophy with epispadias and a wide abdominal defect. We have operated also on a male child in whom the defect of the abdominal wall was extensive. This was closed and the epispadias repaired, the urethra being developed on the dorsum of the penis. A different approach to enlargement of the tiny bladder was decided on in this case. Instead of inserting a plastic mold into the bladder at the time of the initial operation, we planned to attempt to dilate this small, fibrous bladder by using a small penile clamp to retain the urine within the bladder. In this child, however, for various reasons, no type of clamp was satisfactory. It became evident that a further plastic procedure with a view of obtaining continence was necessary.

A flap of skin in the perineal area, with its pedicle just over the anus, was raised; this was of suitable length and size for a urethra (fig. 1, *B*). A fistulous tract then was developed beneath the rectal sphincter and was extended to the dependent portion of the bladder. The cutaneous flap was now pulled up beneath the rectal sphincter and inserted into this tract. With the bladder reopened above, and the use of a mucosal flap, a new vesical neck was made in the floor of the bladder. This mucosal flap was extended to meet the fistulous tract from below. Catheter drainage was maintained with a polyethelene tube. The original vesical neck then was closed proximal to the verumontanum. The bladder at this time—in spite of lack of methods of hydrostatic dilatation—was seen to be much larger and we were encouraged, therefore, to defer the use of the plastic mold. The catheter was removed in approximately 6 weeks, following which the new perineal urethra remained well open. It was rechecked after 6 months and was found to have remained open and apparently was completely lined (there were no tubes made with any of these flaps) (fig. 2).

During a short period when the bladder remained closed dribbling through

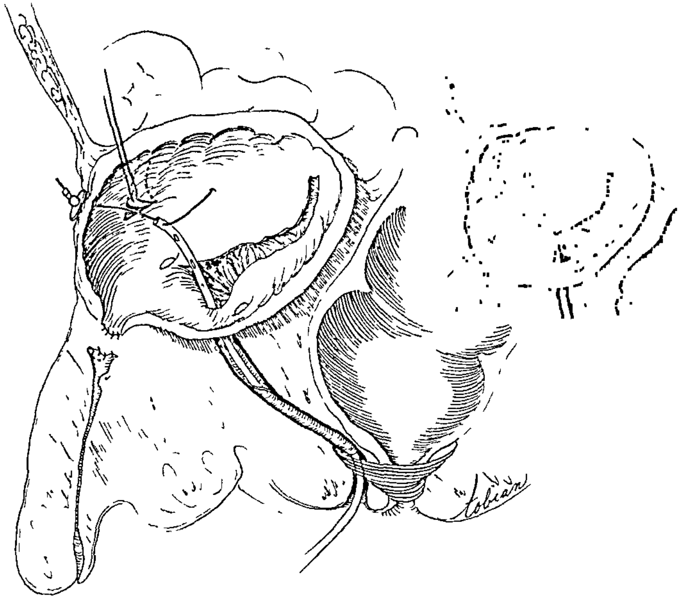

FIG. 2. Repaired bladder without polyethylene mold, illustrating construction of neck of the bladder and perineal urethra Note that bladder and penile urethra are not connected; penile urethra is preserved as an important part of genital tract.

the perineal urethra did not occur. Subsequently a fistula developed through the penile urethra, but when this was held tightly closed and the bladder contained urine, it was noted, again, that dribbling from the perineal urethra did not occur. This observation encourages us to believe that utilization of the rectal sphincter finally may be our best solution to continence.

Incidentally, a somewhat similar plan was effective in providing a satisfactory urethra with continence in a patient who did not have exstrophy but who did have complete incontinence in the presence of a normal bladder.

In the child with exstrophy, just discussed, due to reopening of the old urethra (development of a fistula through the repaired epispadiac penis) deductions as to the end result cannot be made; however, a suitable urinary reservoir has been provided, a good plastic repair has been obtained abdominally, and a perineal urethra has been constructed that is satisfactory as to size—although nonfunctioning. Use of a permanent catheter has been resumed and it is hoped the fistulous tract may close without further surgical intervention. The final outcome as to sphincteric control remains to be determined.

Exstrophy in the female patient. In the female child the vagina in the midline presented a problem. In view of our experience in the three foregoing cases we felt that a suitable vesical reservoir was obtainable in this girl. However, because of absence of any muscle in the area of the neck to be utilized as a sphincter, and since the direct route to the rectal sphincter was interrupted by the vagina, this case constituted a different problem than had previously been encountered. Accordingly, a new vesical neck was made lateral to the left ureteral orifice by a long flap of vesical mucosa with its pedicle at the site of the new neck (fig. 3). This flap was sufficiently long to extend around the vagina and out under the rectal sphincter after a fistulous tract had been developed. Again a small cutaneous flap was utilized (fig. 1, *B*). The bladder was closed and plastic repair of the vulva carried out. An excellent appearance was obtained both abdominally and of the genitalia.

The catheter was accidentally pulled out after only four weeks; however, the child did not dribble. She was at home and the mother reported she was sure that suitable amounts of urine were being passed. When the patient was brought to the office for inspection there was no dribbling but she did have a very wet diaper. The urine had been voided after leaving home (approximately 30 minutes distance). It was not possible to elicit any co-operation from this child because of her age and her continuous screaming and crying when she sees doctors or nurses. It must be considered, of course, that she had never had a full bladder before and did not understand nor interpret it—even if the reconstructed bladder could be presumed to give rise to normal sensations. Unfortunately, the mother did not have a clear understanding of the problem involved. She reported that the child had indicated repeatedly the wish to go to the toilet for a "bowel movement," a habit with which the child was familiar. However, the mother had noted that fecal material was not passed in the majority of instances, but she had neglected to determine with any certainty whether urine was passed at such times. She reported that the child did not cry and was happy and played as usual.

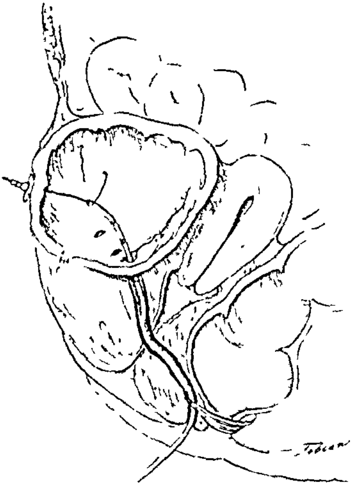

Fig 3. Development of neck of bladder lateral to left ureteral orifice in dependent portion of bladder. This site for new vesical neck was chosen so that there would be minimal distortion of urethra as it extends around vagina and under rectal sphincter. Note that catheter is held in place by tantalum wire that extends through bladder and out through abdominal wall

Within three or four days a fistula developed in the region of the upper portion of the vulva. A catheter then was passed through the perineal urethra without difficulty.

Our experience in this case again illustrates the importance of the catheter being left within the new urethra for at least six to eight weeks so that the wall of the bladder will be well healed and the new urethra become completely lined by the mucosal flap. Anyone who has not worked with children aged two to three years does not realize the great problem of management at this age when a catheter and retention sutures must be maintained for such long periods of time. I feel that the ideal age for procedures of this nature would be approximately one year. I also feel that, at this age, all stages of the operation—regardless of type of deformity—could be done at one time. Subsequently, of course, it might be necessary to carry out secondary procedures to close fistulas, to enlarge persistently contracted bladders and perhaps to aid in urinary control.

DISCUSSION

These initial efforts to devise an improved means of handling exstrophy of the bladder with its varying associated anomalies do not warrant more than preliminary conclusions. It is hoped that improvement and perfection of technique may solve the problem of urinary control.

Several of our colleagues have suggested that even if no more than a suitably large vesical reservoir could be accomplished it would be preferable to ureterosigmoidostomy. In this event a soft, flexible, polyethelene tube ending in the perineum and so designed that it could conveniently be closed and released periodically might be an acceptable and tolerable device. I feel, however, that much further work should be done in the attempt to provide more normal urinary control before resorting to perineal cystostomy as a desirable substitute.

One procedure that may be worthwhile is that contemplated in the male child in whom we have been able to construct a patent urethra in the perineal area, beneath the rectal sphincter. Should we become convinced that this new urethra will not function, we shall investigate the feasibility of connecting it with a short cloaca made from the rectum. I have carried out a similar operation several times in children with urethrorectal or vesicorectal fisulas. This could be accomplished in a manner similar to the Young-Stone technique: The bowel may be freed and amputated in the region of the vesical neck and pulled down underneath the rectal sphincter somewhat similarly to Lowsley's technique which he recently described. It would appear reasonable that the anal sphincter which would completely surround this cloacal urethra would function satisfactorily. According to reports and opinions of colleagues experienced in rectal surgical procedures the modified anus also should function satisfactorily.

SUMMARY

The child with exstrophy of the bladder may have a completely normal body otherwise. When surgical repair of the exstrophy constitutes a handicap to general health, the method of surgical management warrants re-evaluation. Ureterosigmoidostomy—the usual method of treatment—although its initial mortality is low, is followed by considerable overall morbidity and mortality after maturity of the patient. Specific hazards are electrolyte imbalance, ureteral obstruction, renal infection, and metabolic disturbances with inhibition of growth.

Additions to urologic knowledge and improvements and innovations in plastic urologic surgical procedures in recent years may be utilized in combination to provide a better method of dealing with the problem of exstrophy of the bladder and its associated anatomic deformities. Such factors include the following:

Experimental observations in the dog that the bladder will regenerate following surgical extirpation.

Clinical observations in patients with diseased bladders that subtotal cystectomy is followed by vesical restoration or redevelopment eventuating in normal urinary capacity.

The successful plastic repair of hypospadias and epispadias by utilizing a urethral tube constructed from a mucosal pedicle or free flap from the normal normal bladder of the child.

The observation in one case of severe trauma that a urethral tube utilizing mucosa from the patient's normal bladder could be extended through the lower healthy portion of a diseased urogenital diaphragm (below the level of a normal urethra), serving as a normal urethra with satisfactory continence.

Utilization of the lower end of the rectum, separated from the bowel, as a bladder—the anus serving as a urethra with continence In such cases the bowel is reimplanted under the sphincter and functions normally

Employing these principles, we have operated upon 4 patients each representing a different type of exstrophy of the bladder and associated anomalies with the aim of providing an adequate vesical reservoir and urinary continence The technical procedures are described briefly Sufficient follow-up periods have not yet elapsed to warrant a full report of these cases Certain preliminary observations, however, have been discussed

It is hoped that this preliminary report will direct attention to this problem and that further efforts will be made to offer a better outlook to those suffering from this catastrophic urinary anomaly

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TREATMENT OF THE ATONIC BLADDER

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This paper is a preliminary report concerning the treatment of nonneurogenic atonic bladder by total perineal prostatectomy.

The clinical syndrome and the physiological aspects of nonneurogenic atonic bladder were clearly described by Emmett[1] in 1940. Typically, in patients with vesical atony, the bladder has an extremely large capacity, there is little or no sensation with filling, expulsive force is poor, and the urinary residual is large, all without other evidence of neurological disease.

For patients with this syndrome who had little or no prostatic hypertrophy, Emmett advocated transurethral resection of the bladder neck. In 1948 Crabtree and Muellner[2] proposed subtotal cystectomy as a means of eliminating the large urinary residuals which occasionally persist after transurethral resection or open prostatectomy. Fish,[3] in 1950, and Fitzpatrick[4] et al. in 1952, reported additional cases treated by this principle.

In spite of these technical advances, an occasional patient with vesical atony may still constitute a problem in treatment. Large amounts of residual urine may persist after removal of all evident obstruction, after resection of the bladder neck, and even after subtotal cystectomy. One case reported by Fish had a residual urine of 600 cc after subtotal cystectomy and removal of bladder neck obstruction. In a similar case, Griffin[5] observed the redevelopment of a large residual urine. When first seen, the patient was able to empty his bladder completely following a prostatectomy and subtotal resection of the bladder by another urologist 3 months previously. Six years later, the residual urine varied between 600 and 800 cc.

In accordance with my previous observations concerning the role of the urethral musculature in maintaining continence,[6] it seemed reasonable to expect removal of the entire prostate to offer certain advantages in the treatment of vesical atony. The following case is accordingly reported.

CASE REPORT

The patient was a 63 year old man. His presenting complaint was a lower abdominal tumor mass of 3 months' duration which prevented him from fastening an abdominal support he had worn for years. He was also aware of a rather slow

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urinary stream of indefinite duration. A secondary complaint was nocturia of 3 months' duration. There were no other urinary symptoms.

Physical examination revealed a large mass in the lower abdomen. On rectal examination, the prostate was normal to palpation, and the anal sphincter tone was normal. There were no neurological findings. After 400 cc of clear urine were voided, 2300 cc of residual urine were removed by catheter with disappearance of the abdominal mass. Urinalysis was negative. Blood urea and creatinine were normal; 30 per cent of phenolsulfonphthalein was excreted in 30 minutes. Cystoscopy disclosed diffuse, coarse trabeculation of the bladder wall and minimal prostatic hypertrophy. After 30 days of indwelling catheter drainage, transurethral prostatic resection was performed, and 10 gm. of tissue were removed. The patient was unable to void postoperatively, and when catheterized, 1500 cc of urine were recovered.

An indwelling catheter was inserted, and the patient followed for 6 months. During this period, bladder capacity, sensation with filling, and residual were repeatedly estimated, and were found to be essentially unchanged. After the introduction of 500 cc of fluid into the bladder by gravity, the patient had a vague awareness of an ill-defined lower abdominal sensation. Following the introduction of 900 cc, the patient experienced a very mild "sticking" discomfort in the lower abdomen, but no true desire to void. When the catheter was withdrawn, he was able to void 200 cc with 700 cc of residual.

Six months after transurethral resection, total perineal prostatectomy was performed. The tissue recovered weighed 30 gm. After removal of the catheter, the patient was able to void a good urinary stream in the standing position with a residual of 100 cc. Examination 18 months later revealed that the initial improvement had been maintained. The urine was normal and uninfected.

DISCUSSION

The cardinal principle in the treatment of vesical atony is restoration of a balance between detrusor force and urethral resistance. In the presence of a normal detrusor, total or so-called radical perineal prostatectomy reduces urethral resistance to such an extent that some degree of incontinence frequently develops. These observations prompted the use of total prostatectomy in the case reported here, with the result that nearly normal micturition was achieved. This procedure also affords certain other advantages: multiple resections are avoided; major abdominal surgery is unnecessary; complications are few; and convalescence is short.

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AORTIC ANEURYSM CAUSING BILATERAL URETERAL OBSTRUCTION: REPORT OF CASE

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Despite the anatomic proximity of the abdominal aorta to the structures of the upper part of the urinary tract, in only a few reported cases has primary aneurysmal disease of the aorta extended to the kidney or its appendages and caused urographic changes or signs and symptoms of disease of this part of the urinary tract.

It has been pointed out that aortic aneurysms may simulate primary renal or ureteral lesions. Uhle,[1] in an excellent review of this problem, included five representative cases in his paper but in none of these was there ureteral obstruction. James[2] reported a postmortem study of an unruptured aortic aneurysm that involved both renal arteries and both ureters. The renal arteries ran in the wall of the aneurysm and their lumina were greatly reduced in caliber. The ureters were intimately adherent to the aneurysmal wall, considerably narrowed and flattened, but not completely obstructed. The kidneys were reduced to one third of their normal size and there was no dilatation of the calyces. This patient presumably died in uremia but was not anuric or even oliguric.

Howland and Sprofkin[3] reported a case of saccular aneurysm of the aorta that produced terminal anuria. In their case the loss of renal function seemed entirely due to compression of the principal renal vessels. They were unable to find a previously reported case of anuria due to aneurysm.

Dissecting aortic aneurysms[4-6] have been reported as a cause of either unilateral or bilateral renal malfunction. In each case the lesion compromised the renal function by involvement of the renal vessels.

Our case differs from the cited cases in that 1) the aortic aneurysm almost completely obstructed the upper part of both ureters, 2) the renal circulation was apparently unimpaired and 3) a dramatic return of renal function followed diversion of the urine. This case is unique in our experience, and although similar cases may have been reported, we have failed to find any.

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REPORT OF CASE

A 45-year-old white man, a laborer, was first seen at the Mayo Clinic on December 4, 1952 His presenting complaints were vomiting and abdominal pain Obviously seriously ill, he was admitted to a hospital medical service for diagnosis and treatment

Of possible significance was the history of an episode of precordial distress, with extension to the left arm, which had occurred during exertion in 1941 An electrocardiogram was reported as disclosing an abnormal condition at that time

The patient's present illness began in September 1951, when he experienced a sharp, transepigastric pain and nausea immediately following the lifting of some heavy objects This first attack lasted a half hour and was followed on subsequent nights by similar attacks with associated vomiting Two weeks after the initial episode his complaints were investigated elsewhere, after studies failed to reveal the cause of his complaints, he was dismissed with advice to follow a symptomatic regimen The attacks of epigastric pain, however, increased in frequency and severity, occurring both during the day and during the night, until 2 months later when he consulted an osteopathic physician A diagnosis of diverticulum of the duodenum was made by roentgenologic examination, and a laparotomy was performed for removal of this lesion The pain was lessened considerably postoperatively, but the vomiting persisted He was able to return to work in February 1952, two months after laparotomy

In April 1952, the patient noted the onset of bilateral pain at the costovertebral angles, and slight increase in urinary frequency One month later he was hospitalized because he had not felt the urge to urinate and had in fact passed only an insignificant amount of urine over a period of "several" days A urethral catheter was passed but no urine was obtained The urinary output during the first 24 hours in the hospital was only 100 cc despite adequate intake of fluids The value for blood urea nitrogen was 80 mg per 100 cc, for carbon dioxide combining power 35 volumes per 100 cc of plasma, and for blood chlorides 630 mg per 100 cc On the second hospital day the urinary output rose abruptly to 1,500 cc, only to recede to oliguric levels on the third, fourth and fifth hospital days Cystoscopy was then performed and ureteral catheters passed to each renal pelvis Three hundred cubic centimeters of urine were withdrawn from each pelvis Retrograde studies demonstrated bilateral hydronephrosis with dilatation of the upper third of each ureter The hospital course was complicated by Pseudomonas infection of the urinary tract and Pseudomonas septicemia, successfully combated with combined antibiotic and chemotherapy Ureteral catheter drainage was continued for several days The patient voided normally after extrusion of the catheters During this period of hospitalization he experienced an attack of precordial "tightness" with extension to the left arm

Again recovery seemed complete except for occasional tenderness in the left flank, mild frequency and nocturia, and the patient was able to return to his job During November 1952, about a month before admission here, he experienced sudden attacks of vomiting ½ to 3 hours after meals There was a dull ache about and below the umbilicus, and associated constipation The blood urea nitrogen measured 18 mg. per 100 cc. Again symptomatic measures were carried out, but again without benefit, and the patient was referred here for observation and treatment.

Physically the patient appeared well-developed but chronically ill. The blood pressure was 140 mm. of mercury systolic and 90 mm. diastolic. The pulse was regular at 80 beats per minute, and the oral temperature was 98F. The only significant physical finding was the presence of a firm, pulsating, expansile mass, approximately 15 cm. in diameter, just below the umbilicus in the midline. Pertinent laboratory data on admission were as follows: albuminuria, grade 1; pyuria, grade 1; blood hemoglobin, 10.2 gm. per 100 cc; erythrocytes, 3,500,000 and leukocytes, 8,300 per cubic millimeter of blood; blood urea, 152 mg. per 100 cc; carbon dioxide combining power, 12.9 mEq/L; plasma chlorides, 101 mEq/L; sedimentation rate, 127 mm. in 1 hour (Westergren); and Kline flocculation reaction for syphilis, negative. A roentgenogram of the thorax disclosed mild pulmonary congestion. Fluoroscopic examination of the stomach and colon gave negative results. An electrocardiogram demonstrated left axis deviation. Culture of urine from the bladder gave no evidence of growth of organisms. The concentration of blood urea rose slowly to 192 mg. per 100 cc in spite of seemingly adequate urinary output.

When cystoscopic examination was performed on December 15, 1952, the bladder was normal and a 5F ureteral catheter was passed to each renal pelvis with ease. There was a rapid drip of urine from each catheter and since a left retrograde pyelogram disclosed hydronephrosis, grade 3, the ureteral catheters were left in for drainage. During the succeeding 24 hours the total urinary output measured almost 6 liters. The patient's recorded body weight dropped 20 pounds during the next 4 days. The concentration of blood urea, determined daily, fell steadily to 108 mg. per 100 cc during the subsequent 4 days. Bilateral retrograde pyelograms disclosed bilateral pyelocaliectasis, grade 3, and ureterectasis, grade 3, of the upper third of each ureter; the lower two thirds of each ureter was normal. Attempts to re-establish ureteral catheter drainage failed, the urinary output decreased precipitously, and the concentration of blood urea again rose steadily.

There was little doubt in our minds that the pulsating, expansile abdominal mass was an abdominal aneurysm; we were reluctant, however, to attribute bilateral ureteral obstruction unequivocally to such a lesion, inasmuch as we had not previously heard of the occurrence of such a situation. The presence of a retroperitoneal malignant lesion was considered a possibility.

On December 22, 1952, the left retroperitoneal region was explored through an incision in the left flank. The lower portion of the kidney was exposed and mobilized. The kidney was very tense and slightly larger than normal. Extending from the midline, a smooth, tense mass, approximately twice the size of the doubled fist, involved the medial aspect of the lower half of the left kidney, inseparably incorporating within its bounds the pelvis, ureteropelvic juncture and upper third of the ureter. Other adjacent structures and fascial planes were readily separated from the mass by blunt dissection. A definitely visible and palpable expansile pulsation throughout the exposed limits of the lesion confirmed the diagnosis of aortic aneurysm. A trocar nephrostomy was performed at the lower pole, a No. 24 Foley bag catheter being used. After the incision was closed, the patient was turned and the right renal region was explored through a small incision in the right flank. The right kidney was equally tense, and the pulsating mass could be palpated. A trocar nephrostomy was performed on this side also.

The postoperative course was characterized by steady improvement in the patient's general condition. The daily urinary outputs ranged from 1,400 to 2,700 cc, and the concentration of blood urea fell from 176 mg. per 100 cc on the second postoperative day to normal (32 mg. per 100 cc) on the seventeenth postoperative day. Anorexia, nausea, vomiting and pain promptly disappeared, and the gain in strength and the improved sense of well-being were astonishing. He was dismissed from the hospital on the nineteenth postoperative day.

Bilateral pyelograms made through the nephrostomy tubes on the nineteenth postoperative day showed remarkable reduction in the degree of pyelocaliectasis. The completeness of the ureteral obstruction was evidenced by the fact that the patient passed less than 1 ounce of urine through the urethra each day and by the fact that when the renal collecting systems were filled to capacity by gravity, no radiopaque medium flowed down the ureter to the bladder.

Subsequently, abdominal exploration revealed a large aneurysm (measuring approximately 5 by 3 inches) of the abdominal aorta. Both ureters were incorporated in the wall of the aneurysm and were dissected free with great difficulty because of the very marked inflammatory reaction about the aneurysm. Strips of ivalon sponge were placed between the aneurysm and the ureters. Fifteen months later the patient was able to void 1 or 2 ounces of urine once or twice daily, but chills and fever developed within 12 hours after trial occlusion of the nephrostomy tube.

SUMMARY

We have reported a case in which an aneurysm of the abdominal aorta produced bilateral hydronephrosis by nearly complete obstruction of the upper third of each ureter. In this case the resultant azotemia responded quickly to diversion of the urine by bilateral nephrostomy. Ureteral obstruction was due to actual incorporation of the ureter within the inflammatory wall of the aneurysm and not to pressure or displacement. The mechanism by which this unusual condition was produced can, of course, only be postulated: the ureters were probably "caught" in the inflammatory reaction and scarring secondary to leakage of blood from the aneurysm. It seems unlikely that ureteral patency will ever be reestablished in this case.

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CAVERNOUS HEMANGIOMA OF THE BLADDER IN A CHILD: A CASE REPORT

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Cavernous hemangioma is one of the most unusual of tumors occurring in the bladder. This interesting lesion is thought to be congenital in origin. It is typically a slow-growing tumor and histologically is benign except in the rare case of angiosarcoma. Its age incidence ranges from early childhood to old age, and about half the previously reported cases are patients in the first two decades of life. The cardinal symptom of hemangioma is gross hematuria, and the diagnosis is made at cystoscopy, where true hemangioma should not be confused with varices of the bladder. We believe that the treatment of choice is partial cystectomy, which is usually feasible inasmuch as the majority of cases involve the dome of the bladder rather than the base. Very small lesions may be treated by cystoscopic fulguration.

A comprehensive review of the literature is beyond the scope of this paper. Suffice it to say that the first reported case was that of Broca in 1869, and since that time up to 1951 approximately forty-two additional cases have been reported.

Following is a case report of cavernous hemangioma of the bladder in a child, taken from our own practice and representing as far as we can tell the forty-fourth such case in the literature.

CASE REPORT

C. B., an 11-year-old white girl, was first seen in September 1952, with a history of recurring episodes of gross, painless hematuria for the previous 5 months. For the 2 months immediately preceding her initial visit the bleeding had occurred every 3 to 4 days. There was no associated pain, frequency, fever, weight loss, or malaise. The child had not begun to menstruate.

Examination revealed a well-developed, well-nourished child near puberty. There were no abnormalities of the skin and no angiomas noted elsewhere on the body. General physical examination was entirely normal.

A specimen of urine obtained by catheterization was negative for sugar and albumin, and on microscopic examination of a centrifuged specimen there were two to three red cells per high power field. Complete blood count, clotting time, and blood chemistry studies were all normal.

A plain film of the abdomen was negative for opaque calculi, and an excretory urogram revealed normal function and architecture of both kidneys, ureters, and the bladder.

Cystoscopic examination with a 16F Brown-Buerger instrument revealed posteriorly on the right lateral wall of the bladder and behind the right ureteral orifice, an area approximately 5 cm. in diameter in which there were six or seven bluish elevated areas, each averaging 0.5 cm. in diameter. These all appeared to

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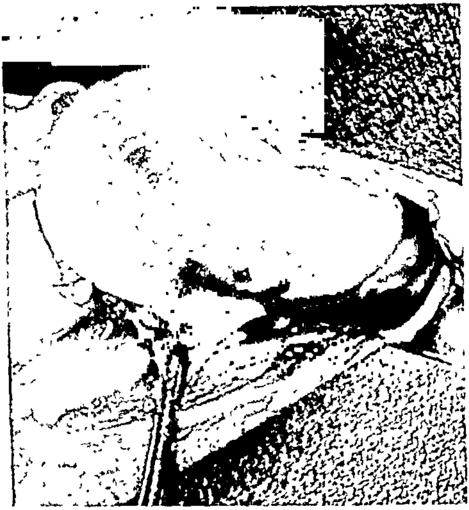

FIG. 1. Photograph taken at operation; hemangioma with bladder open

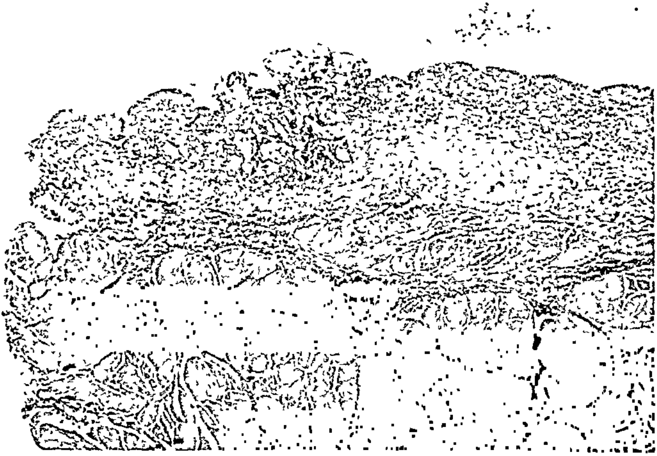

FIG 2. Whole thickness of bladder wall with hemangioma at top

connect with a spiderweb network of blood vessels in the mucosa. The remaining portion of the bladder, including both ureteral orifices and the urethra, was normal. Cystoscopic examination of the vagina revealed a normal cervix and no other abnormalities were noted.

On October 1, 1952, with general anesthesia, a suprapubic cystotomy and partial cystectomy were done, removing the previously described area, which was a slightly elevated, dark blue, cyst-like portion of the bladder wall (fig. 1). The bladder was closed in the usual manner with a small suprapubic drain. Pathological report revealed a typical cavernous hemangioma of the bladder mucosa (fig. 2).

Convalescence was uneventful. Follow-up cystoscopy has been carried out at 6-month intervals since surgery. She was last seen in June 1954, almost two years postoperatively, at which time the bladder appeared normal.

SUMMARY

We believe that cavernous hemangioma should be considered in the complete differential diagnosis of gross hematuria in children, and that the treatment of choice is partial cystectomy with removal of the lesion and a margin of normal appearing bladder wall.

An additional case of this unusual condition from our practice is reported.

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USE OF RADIOACTIVE COBALT (Co_{60}) IN TREATMENT OF BLADDER TUMORS

VINCENT VERMOOTEN

The management of carcinoma of the bladder is one continuous problem. Newer and different methods are always being sought. Recently we have gone so far as to attempt very extensive radical surgery with total excision of all involved tumor but even this has proved unsatisfactory as there is still considerable morbidity and patients still die either from the disease or from the complications and sequelae of the operation.

Two years ago, under the supervision and with the help of Dr. J. G. S. Maxfield and Dr. J. R. Maxfield, we began using radioactive cobalt-containing nylon sutures in the hope of finding a more conservative method of treating the infiltrating type of carcinoma of the urinary bladder which would normally require very radical surgery.

A preliminary report of the first case has been made (J. Urol., **73:** 280, 1955). This is a report of additional cases and of our experience with the use of this new method of radiation.

The use of radioactive cobalt-containing nylon sutures was first described in December 1950, by J. L. Morton, G. W. Callendine and Wm. G. Meyers of the Ohio State University Medical Center at Columbus, Ohio. They used it for neck lymph node implantation and suggested many other possible uses, including using it as an adjunct to the incomplete surgical removal of inoperable tumors. However, they made no mention of its possible use in the treatment of carcinoma of the urinary bladder. In describing the material they pointed out that the wall of the nylon tubing was 0.25 mm. in thickness and that this was sufficient to filter out about 93 per cent of the beta radiation present, making this material, for all practical purposes, a pure gamma emitter. As it gives off only gamma radiation there is no ionization of the tissues and hence a soft, flexible scar results instead of the hard, fibrous scar that follows the ionization when beta radiation is used. In the form of a nylon suture containing cobalt (Co_{60}) the radioactive material can be spaced very accurately and so an excellent radiation pattern can be obtained. It is well nigh impossible to obtain as uniform and accurate a radiation pattern in the urinary bladder with any other form of radiation. It has the additional advantage that it is relatively inexpensive and, as it has a half-life of 5½ years, it can be used over and over again. This material was obtained from the Abbott Laboratories in Chicago through the Atomic Energy Commission.

Our first patient, J. F., aged 45 years, was first operated on and radioactive cobalt implanted into a very extensive infiltrating carcinoma of the bladder on November 20, 1952. Details of this case and the technique of implantation have been described in our preliminary report (J. Urol., **73:** 280, 1955). A recent

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Read at annual meeting, South Central Section of American Urological Association, Colorado Springs, Colo. October 18–20, 1954.

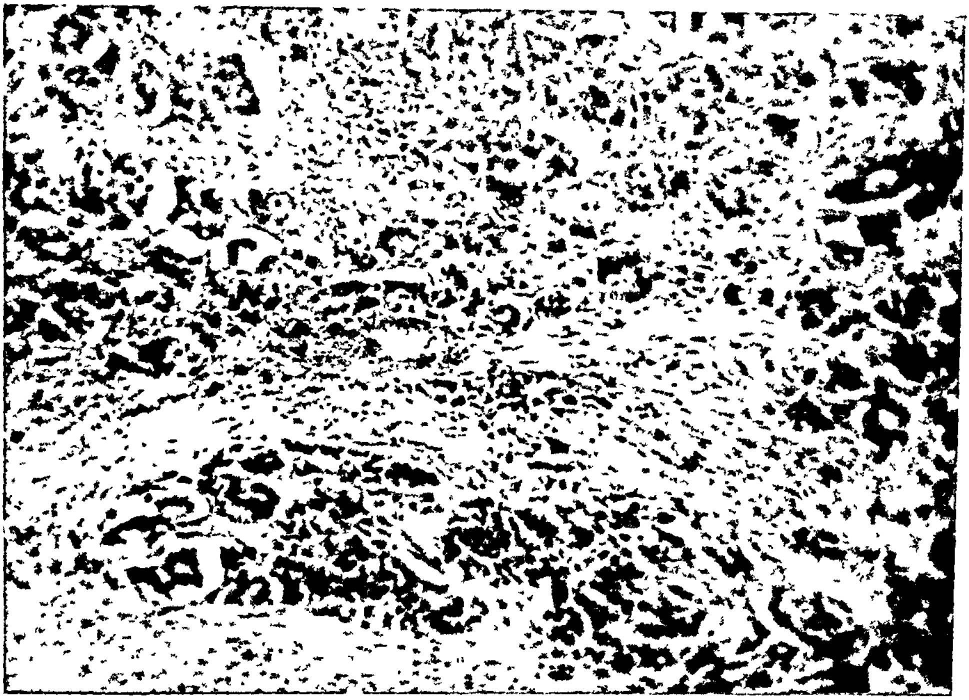

FIG. 1. Case 2. Photomicrograph showing actively invading carcinoma of bladder

follow-up, just 2 years after his first operation, reveals a normal appearing and normally functioning bladder with no evidence of carcinoma and a Papanicolaou stain of his urine sediment reveals no malignant appearing cells. His bladder capacity has increased from 75 cc to 350 cc since his operation.

Our second patient was a 68 year old man (O. H. C.) who was referred to me on October 27, 1953, for cobalt implantation after his doctor had examined him and found him to have an extensive carcinoma of the bladder. He gave a history of having had hematuria for the first time 2 weeks previously.

On physical examination, except for chronic bronchitis and severe emphysema, he was well. Cystoscopically one saw a large, sessile bladder tumor measuring about 2 cm. by 6 cm. in area and raised above the bladder mucosa about 2 or 3 mm. The bladder capacity was 200 cc. On October 28, 1953, the tumor was exposed suprapubically. It was found to be much more extensive than it appeared cystoscopically as it could be felt extending under the mucosa for 2 or 3 cm. beyond the visible tumor. After an adequate specimen had been obtained for biopsy (fig. 1) 8 strands of cobalt$_{60}$ were sewn into the carcinoma. Each strand was parallel to the next and they were spaced about 1 cm. apart. The cobalt$_{60}$ sutures were placed just beyond the place where tumor could be felt on one side to just beyond palpable tumor on the other side (fig. 2). The cobalt was removed November 4, 1953, at which time the patient had received a calculated tumor dose of 8000 gamma roentgens. He was discharged well and went home on November 9, 1953. A letter from the urologist who referred the patient to me, dated April 14, 1954 (five months after the operation) states, "Have just finished cystoscopy on O. H. C. and I personally think he has been cured. He is completely free of symptoms and his urine is normal both chemically and microscopically." He is still well and has a normal bladder with a capacity of at least 350 cc.

Our third patient, F. B. M., a 57-year-old man, was first seen June 6, 1953, because of an episode of gross, total, painless hematuria. Except for a slightly enlarged, smooth prostate which felt somewhat harder than normal, no abnormalities were found on physical examination. Cystoscopic examination revealed a smooth, rounded, flat tumor about 2 cm. in diameter just above the right ureteral orifice. A blood clot was adherent to this tumor. June 11, 1953, the bladder was opened suprapubically. Biopsy (fig. 3, *A*) showed the bladder tumor to be metastatic from a carcinoma of the prostate. A suture of radioactive cobalt was placed around the bladder lesion. A bilateral orchiectomy was done and the patient was placed on estrogen therapy. Six months later the bladder and the prostate appeared normal and cystoscopically one could find no evidence of disease. The area where the bladder tumor had been was normal. Re-examination, a year after the operation, revealed a fungating carcinoma at the internal urethral orifice. The bladder, including the area where tumor had been, appeared normal. Rectal examination with the cystoscope in the urethra revealed a flat, atrophic prostate with no suggestion of carcinoma, so it was assumed that the prostatic carcinoma was fungating into the bladder. The patient was advised to have radioactive cobalt sewn into the "recurrent" carcinoma. On July 8, 1954, the bladder was again opened suprapubically. The bladder appeared entirely normal but at the prostatic orifice a fungating tumor was seen which involved the anterior two-thirds of the orifice. After removing a segment for biopsy, nylon

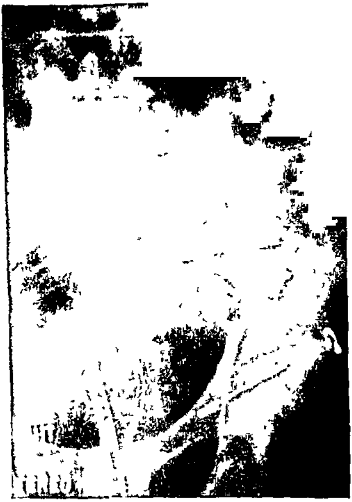

FIG. 2. Case 2. Cobalt pattern

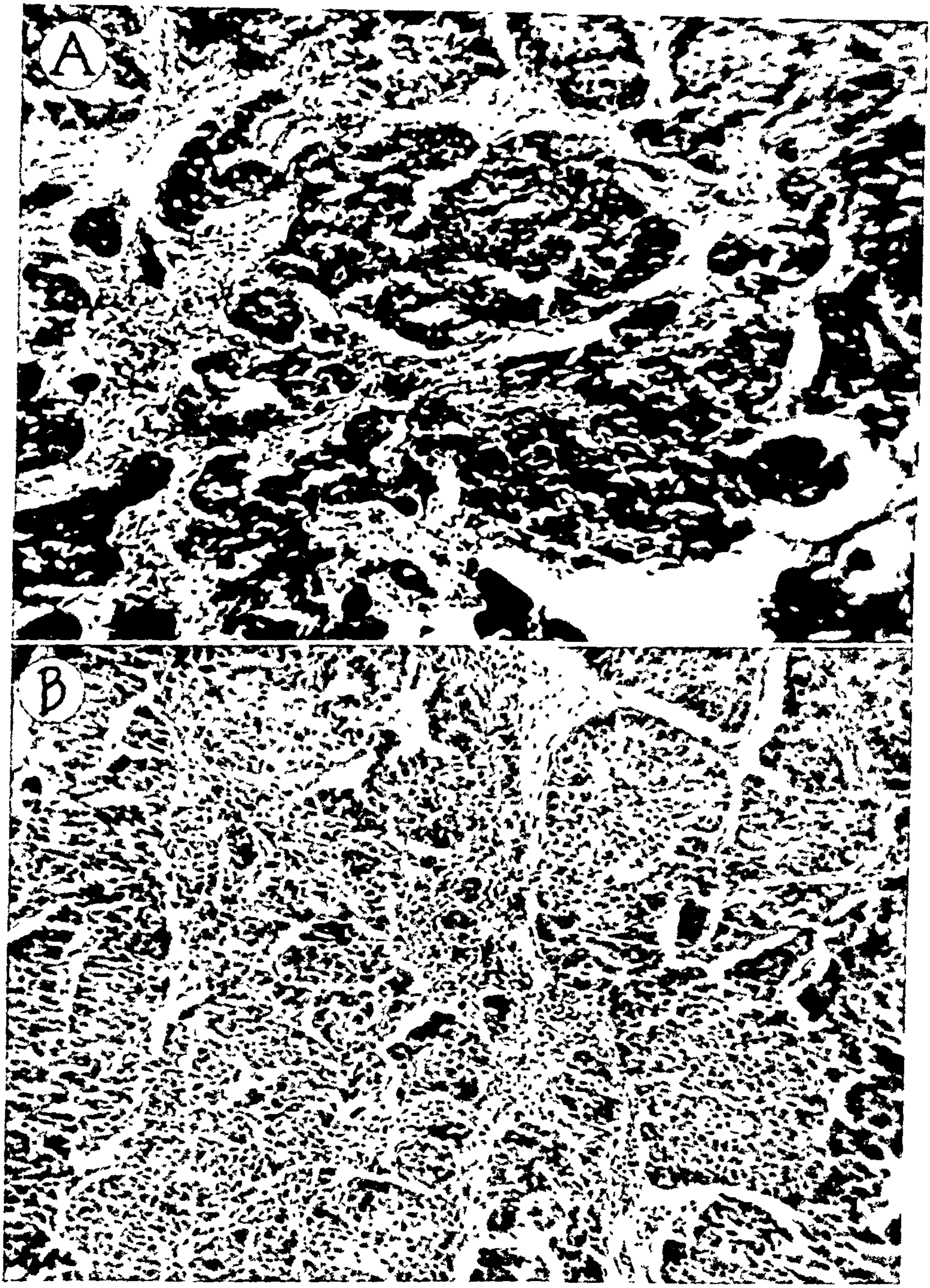

FIG. 3. Case 3. *A*, photomicrograph of biopsy from bladder tumor. Primary gland cell carcinoma (grade 3 to 4) metastatic from prostate to bladder. *B*, photomicrograph showing rapidly growing transitional cell carcinoma. Note totally different structure of tumor from one treated 1 year previously, *A*.

sutures containing radioactive cobalt were sewn through the base of the carcinoma as well as immediately above and below the lesion (fig. 4, *A*). A 30 cc balloon catheter was left indwelling and the bladder closed around a 26F 5 cc balloon catheter. X-ray examination 2 days later showed that with the balloon

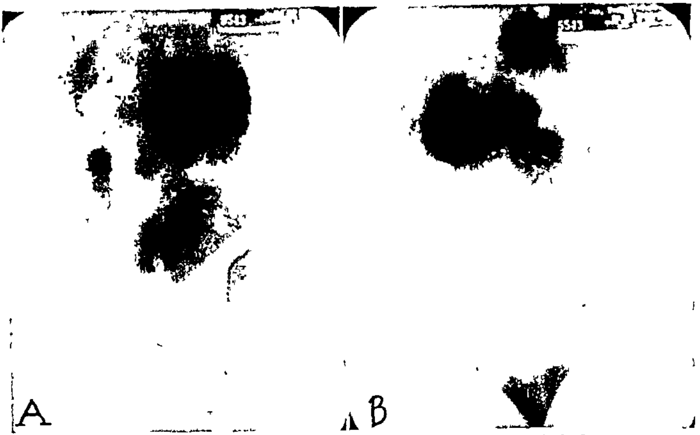

FIG. 4. Case 3. *A*, cobalt pattern with balloon of catheter distended. *B*, cobalt pattern without balloon. Note change in position of cobalt sutures.

deflated there was a better cobalt pattern for effective radiation (fig. 4, *B*). The urethral catheter was consequently removed. On July 15, 1954, the seventh postoperative day, the radioactive cobalt sutures were removed as it was estimated that by that time the patient had received about 8000 gamma roentgens to the tumor. The pathologist reported that the tumor removed for biopsy showed it to be an "infiltrating transitional cell carcinoma of the bladder, grade 3 malignancy" (fig. 3, *B*). This was not carcinoma of the prostate; it was apparently a a new tumor, not a recurrence. Six weeks later the patient still had much frequency and urgency and a small bladder capacity. Cystoscopic examination revealed a diffusely red, edematous bladder mucosa but no sign of tumor. It seemed apparent that the patient had an irradiation cystitis. We assume that this was secondary to the deflation of the balloon. Now, October 8, 1954, three months later, the patient is entirely free of symptoms. He has a bladder capacity of 6 ounces. The urine is normal and on cystoscopic examination one sees an entirely normal bladder with normal mucosa and no scar is apparent.

February 4, 1954, I implanted cobalt in nylon sutures in C. H. Z. He is a 60-year-old man whom I first treated for a papillary carcinoma of the bladder December 1950, at thich time I resected a tumor over the right ureteral orifice. In October 1952, there was a local recurrence. This was resected transurethrally and radon seeds implanted. In January 1954, a transurethral resection showed that the urothelial cell tumor had invaded the prostate (fig. 5). Accordingly it was decided to use radioactive cobalt in the hope of stopping further progress of the disease. Two sutures were placed in the prostate, a third at the junction of the prostate and bladder and two more through the floor of the bladder adjacent to the internal sphincter. The cobalt sutures were removed February 12, 1954, and at that time a piece of tissue at the prostatic orifice was removed with the resectoscope for microscopic examination. Radiation effect but no visible tumor

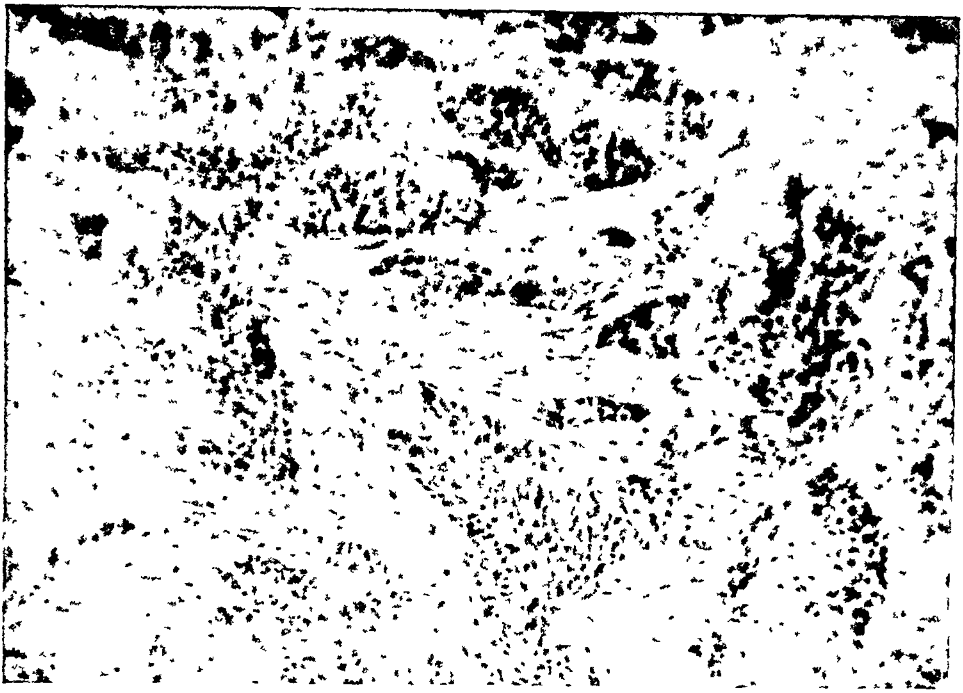

FIG. 5. Case 4. Photomicrograph showing actively invading urothelial cell carcinoma.

was seen. Since that time the patient has had a good deal of frequency, urgency and dysuria. Cystoscopically the bladder shows a good deal of necrotic slough especially around the prostatic orifice and over the trigone. This patient did not have a 30 cc balloon catheter in his bladder, so that it is possible that he got more intensive radiation than was calculated. On the other hand, he had had previous transurethral resections of the tumor as well as implantation with radon seeds. At the time of the insertion of the radioactive cobalt sutures no superficial tumor was seen. The biopsy had shown that a grade 3 transitional cell carcinoma was invading the bladder and prostate although one could see no surface growth either cystoscopically or at operation. This patient died in uremia December 14, 1954. Autopsy revealed bilateral hydronephrosis as well as some residual carcinoma in the prostate, base of the bladder and perivesical tissue.

C. K. B., a 67 year old white man, was first seen July 6, 1954, because of hematuria. Cystoscopic examination revealed a large, papillary carcinoma about 4 cm. in diameter, situated just above and lateral to the left ureteral orifice. The pedicle could not be visualized. The prostate was two to three times normal size and had the characteristics of a benign fibroglandular hyperplasia. The patient was operated on July 13, 1954, at which time the bladder was opened suprapubically. A very large, broad based, pedunculated tumor was removed. The pedicle measured about 1½ cm. in diameter. Two other very small papillary growths were seen. After enucleating about 30 gm. of prostatic tissue, two nylon sutures containing radioactive cobalt were then sewn through the base of the main tumor and carried under the pedicles of the small tumors. A 30 cc balloon catheter was passed through the urethra and inflated, then the bladder was closed around a 26F 5 cc balloon catheter as a cystostomy tube. As the patient had considerable bladder spasm which was greatly relieved by deflating the balloon of the urethral catheter, this was removed on the fourth postoperative day. The patient's suprapubic tube and the cobalt were removed on the eighth postoperative day. The patient's subsequent course has been uneventful. Now, September 16, 1954, about two months postoperatively, the patient is free of symptoms except for some frequency of urination. Cystoscopically there is no sign of tumor. There is still some slight edema at the site where the tumor had been and there is a small area of radiation necrosis near the air bubble at the site where the radioactive cobalt sutures came out beside the suprapubic tube.

C. S. H., a 61-year-old white man, was referred to me because of gross hematuria. For several months he had had recurring episodes of "cystitis" which had been treated with antibiotics and bladder irrigations. Cystoscopic examination revealed a small, contracted bladder with a capacity of only 85 cc. The left half of the bladder appeared normal but the right seemed to be involved in an infiltrating process of some type. The wall of the bladder was obviously thickened and inelastic. The mucosa was velvety red with superficial ulceration. It was felt that this was either an infiltrating carcinoma or an inflammatory process secondary to acute diverticulitis of the sigmoid or to some other extravesical disease process. Papanicolaou stain of a freshly voided specimen of urine was reported to show "atypical cells present classified as representing malignant tumor cells, possibly of gland origin." Barium enema and other bowel studies were normal. Biopsy revealed an infiltrating transitional cell carcinoma of the bladder (fig. 6).

On July 15, 1954, this patient's bladder was opened suprapubically. The

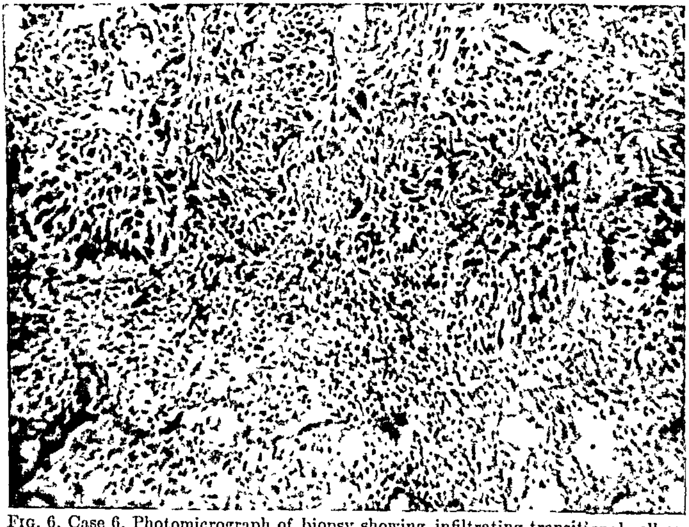

FIG. 6. Case 6. Photomicrograph of biopsy showing infiltrating transitional cell carcinoma of bladder.

bladder appeared normal everywhere except on the right lateral wall where there was a superficially ulcerated area about 2 cm. in diameter. The wall of the bladder was dissected free. No extravesical disease was found. On palpation through the thickness of the bladder wall there was a large area of hard induration, about 1.5 cm. in thickness in the center. The induration involved an area of about 4 cm. by 6 cm. Six strands of radioactive cobalt were sewn lengthwise through this area. The bladder was closed around a 26F 5 cc balloon catheter after a 22F Wheeler catheter with a 30 cc balloon had been left in the bladder. Because of the spasms the balloon of the Wheeler catheter was deflated after 48 hours when x-ray revealed that the cobalt pattern was satisfactory with the balloon deflated. This catheter was removed on the fourth day and radioactive cobalt and suprapubic tube on the seventh postoperative day. Examination 6 weeks after operation revealed that the bladder capacity was 4 ounces instead of less than three, as before the operation. The entire bladder mucosa had a velvety appearance. There was some superficial ulceration at the prostatic orifice where the radioactive sutures may have been too close together after deflating the balloon of the Wheeler catheter. Three months postoperatively cystoscopic examination showed a normal bladder with no evidence of tumor and a bladder capacity of 14 ounces. The site where the tumor had been was indistinguishable from the remainder of the bladder. This tumor mass could have been removed by segmental resection of the bladder but with radioactive cobalt available and with our previous excellent results, we chose this method of treatment.

COMMENT

From our rather meager experience in the use of radioactive cobalt-containing nylon sutures in the treatment of infiltrating carcinoma of the bladder we have learned that this is a very practical and very efficient method of radiating bladder tumors. Maximal gamma radiation can be applied to the tumor without any effect or injury to the remainder of the bladder, provided the bladder is kept distended with an inflated 30 cc balloon catheter. If this is not done, a mild transient radiation cystitis will result. The radiation pattern is uniform so that when the sutures are properly placed, no radiation necrosis should occur. Consequently the bladder capacity returns to normal.

SUMMARY

This is a presentation of 6 cases in which radioactive cobalt-containing nylon sutures were used in the treatment of carcinoma of the urinary bladder. In 5 instances this was used with excellent results in treating extensive carcinoma of the bladder. The fourth patient died from perivesical extension of the tumor. In the fifth case an extensive segmental resection of the tumor may have been adequate and in the sixth a transurethral resection with implantation of radon seeds may have been satisfactory. In 2 cases, radioactive cobalt was used twice; in one patient, 6 months; and in the other, a year after the first implantation.

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THE TREATMENT OF CANCER OF THE BLADDER BY RADIOACTIVE COBALT

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Cancer of the bladder is still a challenge to urology Surgical treatment and radiotherapy as well as combinations thereof have been used extensively In the last years antimitotic drugs have been added to our armamentarium Lasting results remain poor We have to be on the lookout for new possibilities in the treatment of this dreaded disease Radioactive isotopes have aroused the interest of some, as soon as these substances became available

Morton puts cobalt cylinders in nylon threads into the base of tumors of the bladder and urethra during operation Wallace applies wires of radiotantalum in the same way Hinman Jr uses a small sphere of radiocobalt in the midst of a balloon brought into the bladder, while Becker brings a string of radioactive cobalt beads into the bladder through the sheath of a resectoscope

Since January 1951 we have followed in 42 cases a method that Muller has shortly described in 1951 This same method has been used by Mayor in Zurich in about 60 cases with approximately the same results, bringing up the total of cases, in which the method about to be described has been used, to 100 cases Mayor will publish his cases in another connection

Three years is too short a time to judge a treatment for cancer, but it is long enough to get an impression of its value and to find out whether it is worthwhile to continue using it

Work with radioactive isotopes is teamwork The urologist by himself is helpless, he needs the advice and collaboration of the nuclear physicist It is therefore quite natural that this study is split in two parts a clinical part and a physical part, simple enough, so that the urologist can read it, and explicit enough, so that the physicist, should his opinion be solicited, can follow our reasonings

Our thanks go to Alexander von Muralt, professor of physiology and head of the Theodor Kocher-Research Institute and Adolf Zuppinger, professor of radiology in Bern Both gentlemen put all the resources of their institutes at our disposition and never failed to give us help and advice, when it was needed

PHYSICAL PART

^{60}Co is a radioactive isotope of the metal cobalt and can be made conveniently by irradiation of ^{59}Co (a stable isotope comprising 100 per cent of normal cobalt metal) in the slow neutron flux of an atomic pile ^{60}Co emits in series a β-ray of maximum energy 0 308 MeV*) followed by two rays in cascade of 1 17 and 1 33 MeV

Per atomic transition, the ^{60}Co nucleus emits 0 1 MeV in energy of electrons (average energy of the β continuous spectrum) for 2 4 MeV in γ rays The amount of energy emitted as electrons is only 5 per cent of that emitted as γ rays. The nucleus which remains after the β emission is the stable Ni isotope of atomic weight 60. Measurements of Mayneord and Cipriani (1947) have shown that the Co-γ-radiation can be considered monochromatic with an energy of 1.2 MeV, i.e., a wave length of ca. 10 X.U. A silver foil of e.g. 0.1 mm. or a layer of water of ca. 1 mm. is sufficient to cut out the soft β radiation of ^{60}Co. The half-life of ^{60}Co amounts to 5.3 y; therefore, for the short length of a treatment (in our case a maximum of 10 days) a disintegration correction hardly needs to be applied. After a period of one month the activity is lowered only 1.1 per cent.

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* This is the energy acquired by one electron in falling through a potential difference of 1 million volts, this corresponds to an energy of 1 6 10 ^{6} ergs

The dosage rate of ^{60}Co, i.e., the number of r-units which a point source of 1 mC* produce in 1 hour at a distance of 1 cm. is 13.5 r/mC/h. The dosage rate of ^{226}Ra, filtered with 0.5 mm. Pt is 8.3 r/mg/h. One mC of ^{60}Co (unfiltered) gives the same dosage rate as about 1.6 mg Ra filtered with 0.5 mm Pt.

BIOLOGICAL ACTION OF ^{60}CO

The biological effect of ^{60}Co radiation is comparable to that of Ra and high voltage x-radiation. The effect, as is known, is due principally to the ionizing properties of the radiation in the cells. Meshan et al. (1952) tried to compare the biological effect of Ra and Co radiation when they implanted Ra and Co needles in symmetrical places on rabbits. However the authors could not always have the same time factor with the same dose. The experiments show that the radiation reaction with Co is insignificantly greater than with Ra. Also tests with Ra and Co-moulds in rabbits and men show a somewhat stronger radiation reaction with Co. Experiments are now in progress in our laboratory to attempt to carry out these reactions under more controlled conditions.

PREPARATION IN THE PILE

The ^{60}Co at our disposal comes from Harwell, England where an atomic pile is in operation. ^{60}Co is available in metallic form (Co sponge) from which a solution of $CoCl_2$ is readily prepared by treatment with HCl in a water bath. The strongly active solution (we generally had an activity of 200–300 mC) can be preserved for a long time in a special lead container. One should take care that the radiation present at a distance of 1 m from the vessel, is not higher than 10–20 mr/h. Ninety-nine per cent of the Co radiation is absorbed only by a 22 cm. Pb wall or a 45 cm. concrete wall. Yet an air space of 460 cm. reduces the radiation produced by a 100 mC ^{60}Co source to the tolerance level of ca. 300 mr/week. The following tabulation shows several thickness of Pb which are useful in the reduction of radiation produced by ^{60}Co sources of different activities at a distance of 30 cm. to the same tolerance level.

Source of 50 mC	about 7 cm Pb
Source of 200 mC	9 cm Pb
Source of 400 mC	11 cm Pb

These values can be especialy useful for the preparation of the source.

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* Millicurie, that quantity of material which disintegrates at a rate of $3.7 \cdot 10^7$ atoms per second.

ESTIMATION OF THE DOSE

The source which we have used for the treatment are spherical and possess a volume of 50 cc. In several cases the volume had to be reduced to 30 cc. The most important problem for a treatment is the dosimetry of these sources, i.e., the specification of the r-units which a source liberates on the surface and at different distances from it. The problem can be solved mathematically and the results checked chemically. A biological control of the results obtained is in progress at our institute.

Mathematical determination of the dose: Souttar (1931), Mayneord (1945) and Marinelli, Quimby and Hine (1948) have calculated the dosage rate at a point displaced a distance c cm from the center of a sphere filled uniformly with a radioactive substance. The absorption of radiation in the sphere or in tissue is not considered however. It is:

$$D_c = \pi k\rho\left(2a + \frac{a^2 - c^2}{c}\ln\frac{c + a}{c - a}\right). \qquad \text{(in } r/h\text{)}$$

D_c = Dose at a distance c from the center of the sphere in r/h,
a = radius of the sphere,
k = dosage rate for the isotope (in r. cm²/h.mC) at 1 cm from a point source (for ^{60}Co, $k = 13.5$ r.cm²/h.mC).
ρ = density of the radioactive material (in mC/cc).

For the points which are of primary interest in this case, i.e. the dose at the surface, one simply places $a = c$ in the above formula. Thus

$$D = 2\pi k\rho a. \qquad \text{(in } r/h\text{)}$$

Precise data are of course obtained when one considers the absorption of radiation. For Co γ-radiation the weakening effect consists practically entirely of the Compton effect and the scattered absorption whose coefficient in this case is

$$\mu = \sigma_\alpha = 0.035 \text{ cm}^{-1}.$$

A formula which shows the dose at the surface and beyond the sphere was calculated by Oddie (1951) and Minder and Schindler (1952). It reads:

$$D = \frac{\pi k\rho}{c\mu^2}\{e^{-\mu(c-a)}[\mu(c + a) - 1 + e^{-2\mu a}(\mu(a - c) + 1)] +$$

$$+ \mu^2(a^2 - c^2)\cdot[E_i(-\mu(c + a)) - E_i(-\mu(c - a))]\}, \qquad \text{(in } r/h\text{)}$$

$$-E_i(-x) = \int_{t=x}^{\infty}\frac{e^{-t}}{t}\,dt \qquad \text{(Jahnke u. Emde, 1945)}$$

where k, ρ, c and a have the same meaning as above and μ is the absorption coefficient previously defined. For the surface of the sphere ($c = a$) the formula is:

$$D = \frac{2\pi k\rho}{\mu} - \frac{\pi k\rho}{a\mu^2} + \frac{\pi k\rho}{a\mu^2}\cdot e^{-2\mu a} \qquad \text{(in } r/h\text{)}$$

If we calculate the dose which is supplied to the surface of the sphere by a 30 mC solution in 50 cc both with and without consideration of the absorption, we find the following values:

$D = 116\ r/h$ without absorption
$D = 103\ r/h$ with absorption

The difference between the two values is in the order of magnitude of 10 per cent, so that for many practical cases, the simpler calculation is sufficient.

If it is necessary to determine the dose at a large distance from the surface of the sphere, one must definitely consider that tissue absorption plays a part. For example, at a distance of 7 cm. from the surface of a sphere of radius 3 cm., filled with 100 mC ^{60}Co, it causes a 25 per cent reduction in the dose. It is proper, therefore, to include the radiation absorption in the calculation of isodosic curves. In order to shorten a somewhat long and tiresome calculation, we present here a figure (originating from the work of Minder and Schindler—1952) from which the radiation dose in r/h for various sphere radii and distances from the surface can be read (fig. 1).

CHEMICAL ESTIMATION OF THE DOSE

A particularly simple radiation reaction is the oxidation of ferro to ferri-sulfate (Fricke and Morse, 1927), which is used by many authors for estimation or control of the dose. The dosage rate of ^{60}Co, $k = 13.5$ r.cm^2/mC.h, used in the mathematical estimation of dose of a sphere filled with Co, was chemically checked by Minder (1953).

Two experiments were undertaken in which the ^{60}Co solution of 86.6 mC (precision measurements A.E.R.E. Harwell) was placed in a sphere vol. 52 cm.^{3}

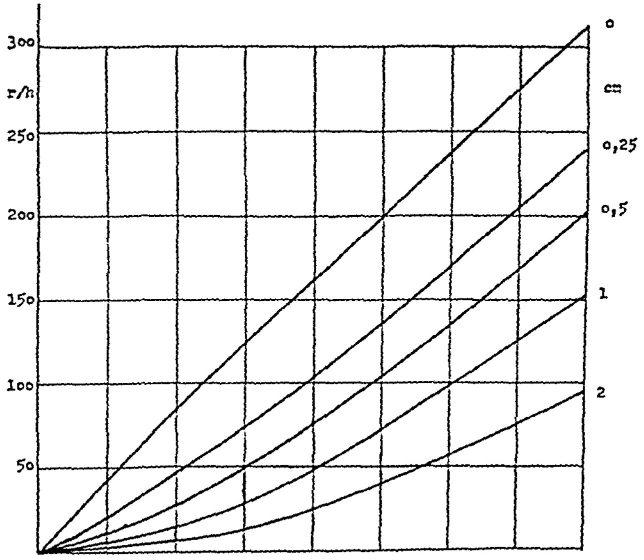

FIG. 1. Dose in r/h as a function of the radius R (max. 4 cm.) and of the distance from the surface (parameter right) for a sphere filled with 1 mC/cm.^{3} (radioactive density ρ) of ^{60}Co.

Example: Sphere of 150 cm.^{3} (R = 3, 58 cm.) filled with 60 mC of ^{60}Co; i.e. $\rho = 60/150$ mC/cm^3 = 0, 4 mC/cm^3.
Surface dose D: for $\rho = 1$ mC/cm^3, D = 280 r/h
for $\rho = 0,4$ mC/cm^3, D = 112 r/h

and surrounded by concentric sphere, in one case radius 3 10 cm , in the second, radius 1 70 cm The space between the two spheres was filled with a solution of $FeSO_4$ (n/500 $FeSO_4$ in 0 8 n H_2SO_4) By this indirect method it is proved that the total amount of energy (calculated with the above k) yielded by the reaction, actually corresponds to the energy converted by the irreversible chemical radiation reaction

DOSIMETRY IN RADIUM-EQUIVALENT-UNITS

For the purpose of radiation therapeutic applications, it is practical to measure the γ radiation of ^{60}Co preparations with reference to the radium equivalent The data concerning the equivalence of the Co source with a definite number of mg of Radium mean that the γ radiation of the preparation produces the same ionization as the specified amount of radium

Both sources can be compared with one ionization chamber Since the Co source is spherical (50 cm^3 in our case) and the radium source, in most cases, is in the form of needles, one must consider that only at a distance of about 30 cm from the ionization chamber can both source be regarded as "geometrically identical" with respect to dose In addition it should be noted (Muller 1949) that the radium equivalence data are dependent on the filtration with which the source comparisons are made

Finally we would like to point out that this procedure presents no true "dosimetry" of Co sources, it gives no data about the radiation energy transmitted to one point of the tissue Radium equivalence data are often an essential point for the practicing radiologist from which he can draw certain conclusions, however they should never replace the mathematical-physical or chemical dosimetry.

PRACTICAL APPLICATIONS

The treatments have been carried out as follows: a ^{60}Co source which showed the desired surface dose, calculated according to activity (calibrated in Harwell, England to ±5 per cent), was placed in liquid form in a glass sphere of known volume Using such a standard source and an ionization chamber (with an electronic amplifier or an electrometer as a null indicator in a null method measurement) it is possible to prepare the necessary source for the treatment, or to bring a source, which has already been used, to the desired activity As a matter of fact an exchange of ions is possible through the rubber wall of the balloon-catheter during the treatment and a small amount of Co solution always remains trapped in the catheter when it is emptied after We found that the amount of active Co^{++} ions reaching the urine through the catheter membrane never exceeded 10^{-4} μ C per liter urine Only in one case did an extremely small amount of these active ions reach the blood stream This amounted to 1 μ C, so that even in this case, the active level in the body hardly attained the recommended maximum permissible level of ^{60}Co (established by the International Commission for Radiological Protection, 1950)

PRECAUTIONS

The patients were treated in a room as isolated as possible The amount of radiation received by the personnel was measured constantly by pocket radiation

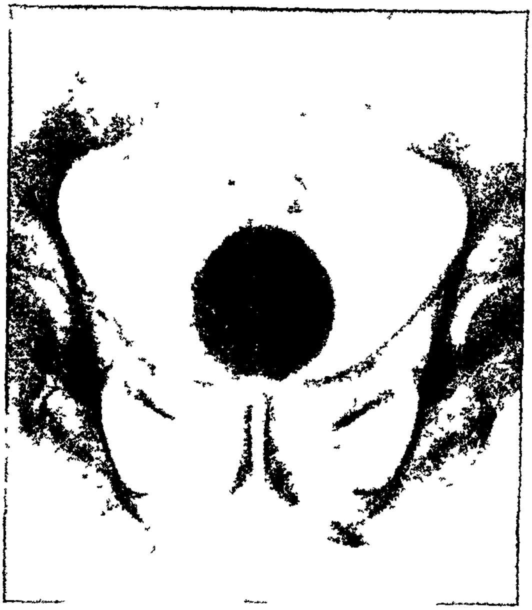

FIG. 2

dosimeters and film badges. The daily tolerance dose of 60 mr was never halfway reached by the personnel, even in the case of patients requiring much care.

CLINICAL PART

The method in itself is simple enough. A 50 cc bag catheter is introduced per urethram into the bladder. Only local anesthesia is required. The question of the catheter is of paramount importance, as we will see in the later discussion. An experimental model, very kindly made on our request by C. R. Bard, Inc., Summit, N. J. gives us entire satisfaction. The balloon is distended to 50 cc by injecting a mixture of water, x-ray contrast medium and indigo carmine. In shrunken bladders we were able to get good results by concentrating our cobalt solution to 30 cc. The catheter is left indwelling up to 24 hours to check its function. An x-ray shows us its correct position in the bladder (fig. 2); the indigo carmine would dye the urine in blue, should the balloon have a hole. If this preliminary period is satisfactory, the mixture is left dripping out, and the cobalt solution introduced under the usual precaution in radioactive work. We found a 3-way syringe, protected by a leadwall convenient (fig. 3). The cobalt solution gives off 3,000 r at its surface and is left indwelling for 10 days, giving us a total dose at the surface of the balloon of 30,000 r At a depth of one inch, we have approximately 25 per cent, giving us 7,500 *r* for the pedicle. This dose is enormous and we have suspected errors in dosage. Checks and rechecks have confirmed our calculations and we have to accept these figures as being correct. This dose has been arrived at empirically in the course of 2 years, starting with a total dose of 4,000 r at the surface of the catheter, for the first cases. It seems to be the maximum dose permissible for the healthy bladder mucosa and causes some reaction in every case. Blood counts are done every 3 days and the radioactivity

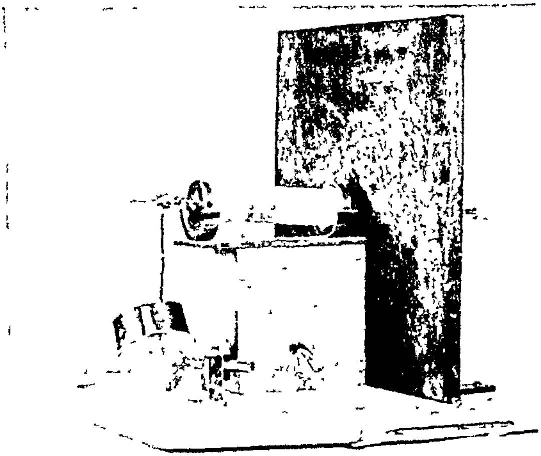

FIG. 3

of the urine checked daily. The precautions for the nursing staff are described in the physical part.

After the treatment all linen etc. is examined for radioactivity and eventually destroyed and buried.

DISCUSSION

At the beginning we treated every patient with bladder cancer coming under our observation with this method. However we soon found out two things: Used for palliation only, the method is ineffective. In hopeless cases that look forward to a survival of not more than 3 months, the reaction to the treatment, the elimination of necrotic tissue, weigh more than the palliation offered afterwards. It is unwise to treat large tumors with cobalt radiation only. The pedicle gets insufficient radiation, large parts of the tumor slough off, infection flares up. All these drawbacks can be avoided by combining surgery and radiation. Either transurethrally or by open surgery all the exophytic parts of the tumors are removed; should partial resection of the bladder be feasible, it is naturally done, even if incomplete. Since the start of this treatment we have not done a single cystectomy for cancer. Radiation may follow surgery immediately, if surgery has only been minor. More often we prefer to wait for the healing of the wound, both in the interest of the patient who gets a smooth recovery, as of the nursing staff who get less radiation from a patient who needs no dressing, postoperative care and so on. We have had no mortality whatsoever from the treatment up to now. The only hospital death occurred in a patient 3 weeks after the treatment from perinephric abscess in a single kidney and uremia.

If the catheter drains well and the patient has no retention and spasms, the period of the treatment is not too painful. The first days go by smoothly. From the sixth day on begins a certain irritation; irritation of the urethra by the rather large indwelling catheter (22F), irritation of the bladder by radiation. Towards the end a disagreeable proctitis may develop. These symptoms usually subside in a week following the end of the treatment; in a minority they may last 4 to 6 weeks. We have had 3 patients in whom the reaction was so severe as to make them badly suffer and incapacitate them for some months. In two of these cases the fatal outcome showed that our diagnosis was erroneous; they did not suffer from a prolonged radiation reaction, but from a spread of the cancer. One case is still under observation. Mayor has had 2 cases of shrunken bladder after cobalt treatment. Total cystectomy showed that no cancer remained. There were no special operative difficulties.

The question of the catheter merits the greatest attention, not only for the sake of the comfort of the patient. If there is retention, the patient suffers severely from spasms, the urine pushes the bladder wall and the tumor away from the surface of the balloon; there is no knowing how much radiation the tumor really gets (fig. 4).

Two reproaches can be made against the method used by us. First, the use of radioactive solutions is too dangerous. There is no doubt, that spilling a highly radioactive solution with a halflife of 5, 3 years could have serious consequences. Every care has to be used to prevent this and manipulation of the radiocobalt cannot be left to a junior houseofficer, but has to remain in the hands of a competent person. The most serious accident that can happen, has happened to us. Shortly after a partial resection of the bladder, the balloon containing the radioactive solution broke. The accident went unnoticed for a few hours and there was some resorption through the wound. The blood remained radioactive for 2 days; elimination occurred by way of the bowels and the urine. The patient had a very stormy convalescence with wound infection, phlebitis and pulmonary embolism. The reaction of the bonemarrow was normal throughout and today, 2 years after the accident, no bad effects can be found in the patient.

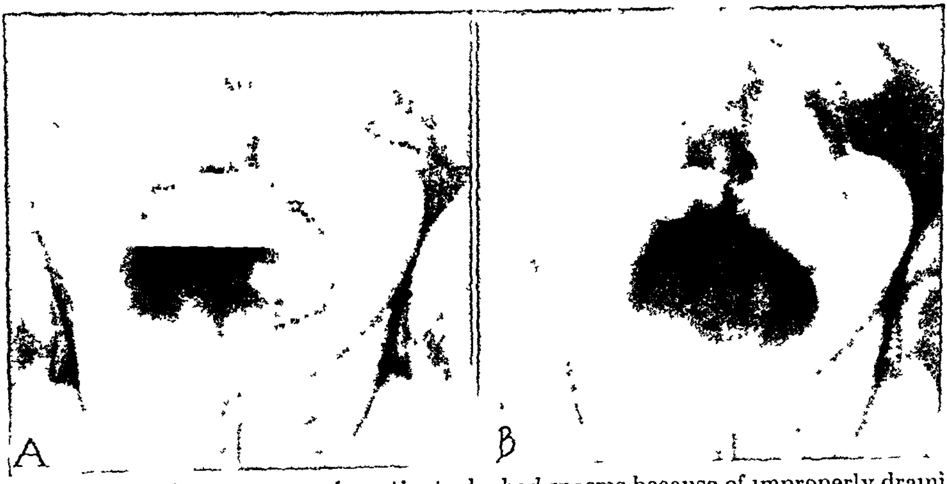

FIG 4. *A*, excretion cystogram in patient who had spasms because of improperly draining catheter Bladder is quiet in illustration. Cobalt balloon is plainly visible. *B*, after spasm. Bladder still incompletely emptied.

The second reproach to be made against our method we have to accept: The irradiation is not selective enough. The healthy parts of the bladder mucosa get the same amount of radiation as the tumor. We are trying to change this by a change in our technical setup, but do not know yet whether we will succeed.

RESULTS

We have treated 42 cases between January 1, 1951 and January 1, 1954. Five of them had two treatments. Three of them had papillomas, all the others carcinomas of the bladder, grade 2–4. Some had metastases at the time of treatment.

Seventeen died, most of them from a spread of the disease, some from metastases with apparently healthy bladders (no autopsy). Nineteen are alive, but still show some cystoscopic evidence, either of tumor or of radiation reaction and a proper evaluation is not possible. Some of them, we hope, will develop towards a good result (this is particulary true for those treated recently with heavy dosage); others will develop towards a fatal outcome.

Six seem to-day to be cured. Their bladders are normal and show no sign of tumor or inflammation. The apparent cure lasts from 6 months to 3 years.

We therefore find a percentage of apparent cures of 15 per cent which is still poor, but compares with total cystectomy. I once more attract the attention to the fact, that the 29 patients treated in 1951–52 we consider to-day as having been insufficiently treated and that we will probably have better results with our present dosage. Cures from cancer of less than 5 years' duration have no great value. I renounce giving the case histories of the apparent cures in detail and limit myself to one single observation that in my opinion proves the efficiency of the method.

A 69-year-old peasant entered the hospital in May 1953. Examination showed a mass in the region of the left orifice and large left hydronephrosis. Transurethral resection removed 10 gm. of tumor, which histologically was papilloma with transition to carcinoma. Irradiation with 30,000 r. Control end of August

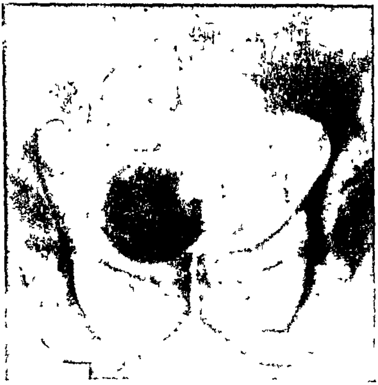

FIG. 5. Bag of catheter displaced to right by infiltrated bladder wall; on left side, tumor has been resected transurethrally, first irradiation about to start.

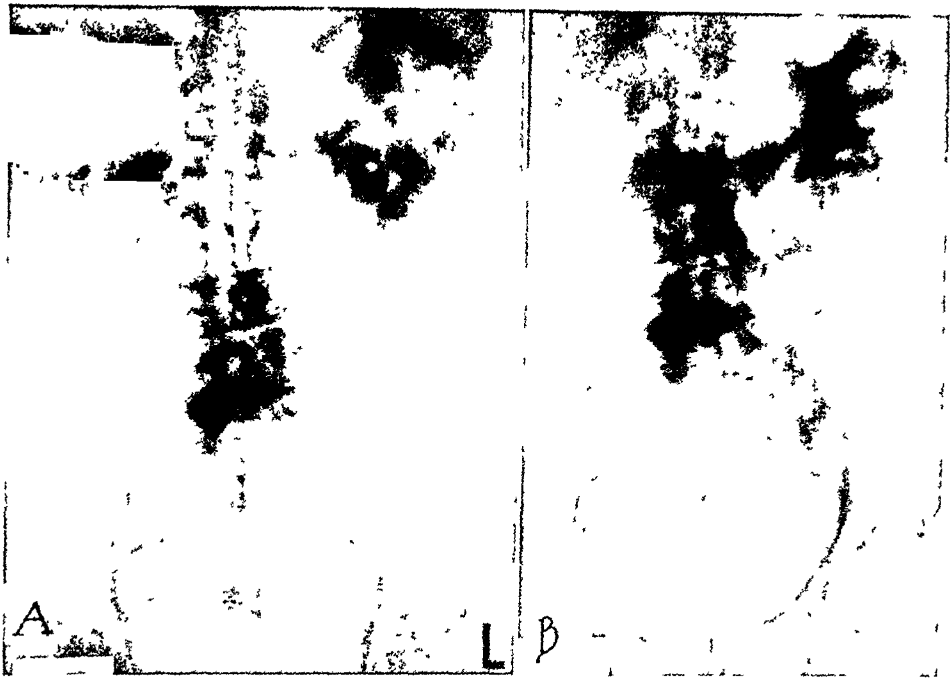

FIG. 6. *A*, large left hydronephrosis. *B*, same patient 3 months after irradiation with radiocobalt (30,000r). Hydronephrosis has disappeared.

showed a new tumor; the hydronephrosis had disappeared (figs. 5 and 6). This time the patient was treated by open surgery (removal of the tumor) and a new irradiation with 15,000 r. This was the largest dose ever given. Cystoscopy November 1953 showed no irradiation reaction, but still a necrotic patch at the base of the old tumor. This patch had disappeared in March 1954. The hydronephrosis was certainly due to infiltration of the intramural part of the ureter by the tumor, its disappearance to a regression of that infiltration which can only have been due to the radiocobalt. (This case is not listed as a cure.)

SUMMARY AND CONCLUSION

To evaluate a method that claims to cure cancer takes a long time and a great deal of effort. The radiation method we have presented seems to us worthy of that effort. In our hands it has proved to offer a cure in some cases (15 per cent) of malignant cancer of the bladder without any mortality and comparatively little morbidity. It is our ardent wish that this method gets a fair tryout by our American colleagues. It is certainly never going to be *the* method in treatment of cancer of the bladder, but we think that it is going to take an important place in a complex plan of treatment, comprising surgery and different methods of irradiation. Before trying out new combinations, we wanted to make sure of the efficiency and required dosage of radiocobalt; we think that 30,000 r are the optimum.

Different ways seem open to better our results: preoperative radiation, followed by extensive surgery; palliative surgery, followed by a combination of radiation methods: for example, cobalt combined with infiltration of the tumor base with radiogold or cobalt combined with high power external radiation by the betatron or beta-synchrotron. We have started trials in this direction with the help of a Brown-Boveri 31 million volt betatron.

Note. In the 12 months since writing of this study, 3 more of the 12 cases described may be accepted as cured. None of the 6 cured has had a recurrence. This makes a total of apparent cures of 21 per cent.

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In addition, conversion of cortical hormones to androgens may occur in the liver and in other tissues.[19, 20] The administration of large doses of cortisone to females with intact adrenals frequently results in acne and hirsutism.[18, 21] Following the administration of large doses of cortisone to people with intact adrenals or moderate doses to Addisonian patients,[21, 22] there is observed an increase in the urine of 17-ketosteroids and their intermediate precursor compounds (steroids with an alpha ketol side chain at carbon-17). In castrated adrenalectomized prostatic carcinoma patients, urinary active androgen excretion varies as the cortisone dosage. It also roughly parallels the level of 17-ketosteroids in the urine. Nevertheless, the urinary excretion of biologically active androgens, even after very large doses of cortisone (300 mg. per day), is less than that of normal men.[21, 23]

Total adrenalectomy has a nonspecific inhibitory effect on the rate of tumor growth of certain transplantable carcinomas and sarcomas in rats and mice.[24-28] Lymphoid tumors, on the other hand, respond with opposite effects. Following adrenalectomy the incidence of "takes" of transplantable lymphatic leukemia was increased and survival time decreased in successfully inoculated rats.[29] There is an increased incidence of spontaneous lymphatic leukemia in susceptible mice following adrenalectomy.[30] The 11-oxygenated corticosteroids can inhibit the growth of certain tumors temporarily. This has been observed in transplantable lymphosarcoma in mice,[31] the Walker carcinoma in rats[32] and in certain osteogenic sarcomas in mice.[31]

In humans the administration of cortisone or ACTH has produced a temporary regression of some lymphomatous tumors. All tumors recurred and had either a diminished or absent response to repeated therapy.[33] In man, cortisone has not caused demonstrable regression of tumors other than lymphomas, even though a feeling of well being, increased appetite, improved strength and a recession of fever are commonly noted.[34, 35, 36]

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TABLE 1. *Preoperative status of patients*

PATIENT	AGE	PREVIOUS THERAPY	EXTENT OF DISEASE	CLINICAL STATUS	ACID PHOS.	ALK. PH
E. N.	53	Castration; estrogens (no response)	Local disease, extension lymphatic metastases	Urinary symptoms, lymphedema rt. thigh with pain	0.6	5.6
S. S.	55	Castration; estrogen; TUR (no response)	Local disease, skeletal metastases	Bone pain, urinary symptoms	0.4	19.6
C. W.	61	None	Local disease, compression fracture L. skeletal metastases	Bone pain	2.8	27.2
K. S.	65	Castration; estrogens; TUR (good response)	Local disease, skeletal metastases	Urinary symptoms, bone pain	1.4	25.9
E. F.	65	Castration; estrogens; TUR (good response)	Local disease, skeletal metastases	Urinary symptoms, bone pain	0.1	11.4
H. B.	49	Castration; estrogens (good response)	Local disease, skeletal metastases	Bone pain, urinary symptoms	0.7	3.9

A metabolite of adrenal cortical origin, 11-Hydroxyetiocholanone, appea in the urine of a significant number of patients with neoplastic disease, where it is rarely found in the urine of normal individuals. Abnormal amounts of no mal steroids have also been demonstrated in the urine of patients with variou cancers[37, 38] This indicates adrenocortical dysfunction, the exact significance which is unknown at present.

RESULTS

Six patients with active disseminated prostatic carcinoma were adrenalec tomized (table 1). Five had previous castration-estrogen therapy. One had n previous therapy. Objective criteria to measure the course of the disease proces were body weight, hemoglobin, acid and alkaline phosphatases, and the siz of either the primary or the metastatic lesions, or both. Changes in activity wer considered as depending on both the course of the disease and upon subjectiv factors.

Five patients are living 356, 342, 200, 82 and 67 days respectively followin operation (table 2). Two patients were unaffected by adrenalectomy, one died 9 days postoperatively and one is still living 67 days postoperatively.

Excellent subjective improvement was noted in 4 cases and objective improve

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TABLE 2. *Effects of adrenalectomy*

PATIENT	POST OP. SURVIVAL DAYS	STATUS	CAUSE OF DEATH	RESPONSE	
				Subj.	Obj.
E. N.	60	Living		0	0
S. S.	90	Dead	Carcinoma	+	0
C. W.	85	Living		+	+
K. S.	198	Living		+	+
E. F.	333	Living		+	+
H. B.	355	Living		+	+

ment in 3 of those cases. Two patients had partial vesical neck obstruction which was relieved following adrenalectomy. Relief in one was temporary, lasting 9 months. The other has no obstruction 11 months to date. Three patients had definite regression of the primary tumor mass. In 2 patients the regression has lasted 11 and 3 months respectively.

Two patients had elevated preoperative acid phosphatase values which dropped to normal levels after adrenalectomy. The values are still within normal limits 90 and 330 days postoperatively. However, the latter patient had no additional signs of objective improvement. Weight gains were noted in 2 patients (4 and 5 kg. following adrenalectomy).

Four patients had significant subjective improvement with relief, especially, of bone pain. Two of these 4 had been bed-ridden with pain unrelieved by opiates. Both were ambulatory within 3 days following operation, although one had substantial but not complete pain relief. His pain has returned recently but is of much less intensity than formerly. Three patients were completely free of pain within 48 hours following adrenalectomy, including one with a compression fracture of the first lumbar vertebra. Pain relief is complete 330 and 90 days respectively in 2 patients. One other patient, who had 270 days of excellent subjective improvement, recently had partial return of his bone pain.

DISCUSSION

Some reactivated prostatic carcinoma in castrated estrogen treated patients responds favorably to adrenalectomy with subjective and/or objective improvement.

The nonspecific inhibitory effect of adrenalectomy on the rate of tumor growth observed in certain animal carcinoma and sarcoma may be present also in adrenalectomized humans with tumors. However, no regression of size in experimental animal tumors was ever reported. Retardation of growth rate would be extremely difficult to evaluate in humans. One could not distinguish between results of therapy and between tumor behavior as dependent upon the biologic potential of the tumor. Miscellaneous tumors in humans, excluding breast carcinoma, prostatic carcinoma, and lymphomas, were unaffected by adrenalectomy.[37, 38]

It is probable that the further elimination of androgenic substances is the main cause of favorable response following adrenalectomy in human prostatic cancer.

Huggins and Bergenstal,[39] West[40] and Harrison[13] have reported the effects of cortisone administration on prostatic carcinoma patients in relapse after previous castration estrogen therapy. Cortisone has produced subjective improvement. It was of shorter duration and not so complete as that following adrenalectomy[37, 38, 13] No objective improvement had been observed[37, 38, 13] until recently. However, in one patient unresponsive to castration and adrenalectomy, massive doses of cortisone produced evanescent subjective relief and a temporary drop in acid phosphatase.[13]

Subjective improvement following adrenalectomy did not parallel objective improvement. A dissociation between relief of bone pain and steady progression of skeletal metastases was observed. This has been noted by other investigators.[37, 38]

Huggins[37] has divided prostatic carcinoma patients into 3 groups depending upon their response to castration estrogen therapy. In the first is found the majority of the patients who respond with regression of the primary tumor and the metastases. In the second is found a smaller group, responding with regression of the primary tumor only. And in the third is the smallest group with no response at all.

Responses following adrenalectomy may be classified similarly but the relative size of the groups appears quite different from that following orchiectomy. In none of our patients did we see regression of the metastases. Of the 23 cases recently reported in the literature[12, 37, 38] only 2 had regression[13] of and one arrest[38] of the metastases.

Our 2 cases without improvement had a poor response to orchiectomy. Harrison[13] reported one similar case. However, one can find in the literature 2 cases[13, 37] with a favorable response to adrenalectomy following poor response to castration estrogen therapy.

These observations are consistent with our present knowledge of the behavior of prostatic carcinoma, especially in regard to response to endocrine therapy. Clinically and experimentally prostatic cancer shows great variation in response to estrogen and after varying periods of growth becomes tolerant of estrogen. Biologically the longer it grows, the more independent it becomes of hormonal environment.[41] This may explain the much smaller number, proportionately, of adrenalectomized patients falling into groups 1 and 2, especially group 1 of Huggins' classification.

The effects of castration on prostatic carcinoma are variable and supplemental estrogen may control some prostatic cancer not affected by castration alone. Experimentally androgen is needed to initiate the growth of prostatic carcinoma though the amount needed may be small.[41] Good response to adrenalectomy following poor response to orchiectomy is probably due to the reduction of androgens below a certain critical level particular to the cancer cells at that time. It is well known, however, that the physiology of the individual cancer cell can change in successive generations both in transplants and in humans.[41] Thus the biologic potential of the individual cancer cell makes it impossible, at present, to predict the efficacy of hormonal therapy on an individual basis.

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SUMMARY AND CONCLUSIONS

Six patients with prostatic carcinoma underwent total adrenalectomy. Five had previous castration-estrogen therapy. Two patients showed no response. Four obtained subjective improvement and 3 objective improvement. Improvement is temporary.

Until more data are acquired and evaluated, total adrenalectomy for prostatic carcinoma remains an experimental procedure.

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UNDIAGNOSED, GROSS RENAL BLEEDING

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Most of the etiological factors giving rise to hematuria can be identified with present day diagnostic facilities. Fundamental to the utilization of mechanical aids to diagnosis must be the acumen of the searcher. Despite the most favorable co-ordination of physician and technical equipment, unsolved bleeding from the urinary tract all too frequently confronts every diagnostician and surgeon. Until better indices as to *benign* blood loss be evolved, useful renal parenchyma will perforce be sacrificed surgically in an honest attempt to ablate neoplasms early in their development.

No less than 15 separate conditions are listed by Lowsley and Kirwin as productive of hematuria.[1] Higgins diagrammatically indicates 36 lesions at various levels in the urinary tract that may account for the presence of erythrocytes in the urine.[2] This author emphasizes the imperious need for complete urological investigation in every instance of hematuria. In this review of 1600 cases of hematuria, he reports that an average delay of 2½ years elapsed between the first appearance of blood in the urine and the opportunity by a physician to establish the diagnosis. The most common forms of pathological process encountered as the basis for hematuria in his study are, in order, tumor, calculi, tuberculosis, infection and nephritis.

It is obvious that the incidence of a primary cause for urinary bleeding would vary with the type of case most frequently attended at any given, specialized clinic. However, the fear of overlooking an early malignancy stimulates urologists everywhere to conduct an exhaustive examination of every patient who presents this problem.

In recent years, Papanicolaou stains of the urinary sediment have proved of value in detection or corroboration of small (and thus, potentially curable by surgery) urinary tract neoplasms.[3, 4] Nonetheless, many tumors escape notice by this technique and are later recognized either radiographically or by biopsy of distant and often unusually located metastases.[5, 6, 7] Since no radioactive element specific for tagging abnormally located red blood cells within the body is known, this method of bleeding site differentiation cannot be exploited at the present time. In essence, the time-honored avenues of urological study, namely, physical examination, urinalysis, cystoscopy and pyelography comprise the tools

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for determining the cause of hematuria. More recently, aortography[8, 9, 10] and retroperitoneal pneumography[11] are finding places in the urologist's diagnostic armamentarium.

Mention in the literature of occasional and unusual cases of "obscure bleeding" from the kidneys or elsewhere in the urinary tract[12] fails to offer improved diagnostic measures.[13] Thus far, in this paper, all the procedures cited as diagnostic aids seek to obviate the use of open surgery. Weyrauch, Wanless, Goebel and Scott urge surgical exploration and biopsy of the kidney for suspected neoplasm before removal of this otherwise usefully functioning parenchyma.[14] Certain objections may be directed against their proposed method, such as the inherent danger of wound implantation of tumor cells at the time of positive surgical biopsy. Moreover, it is unfortunately almost a truism that kidney exploration commits the operator to extirpation when persistent doubt prevails in the operating room as to the nature of the lesion which produces hematuria.

The shortcomings of the entire gamut of diagnostic efforts in some instances of hematuria, even after the most thoroughgoing study, pose the problem for presentation of this communication. It is hoped that our addition of such cases to those already published may act as further stimulus for search of accurate, dependable, preoperative diagnostic methods. It is readily admitted that this report fails to suggest any such advance.

CASE REPORTS

The cases of renal bleeding selected for this study met in common the following basic criteria:

1) Blood was seen to spurt from a ureteral orifice during cystoscopic examination.

2) No renal disease could be discovered by intravenous and/or retrograde pyelography.

3) Absence of urinary infection was proved by bacteriological culture or by stained smear of the catheterized urinary sediment.

4) No hypertension or albuminuria was present.

Table 1 represents a summary of the salient features of 19 cases in which the cause of the renal bleeding was undiscovered. There were twice as many males (13 cases) as females (6 cases) in this series. Eleven Caucasians and 8 Negroes* were encountered. No age group appeared to be more frequently involved than another; the range was from 17 to 66 years. However, 14 of the 19 patients were under 45 years of age, representing a proportion of 73.7 per cent. Equal incidence

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* None of the Negro patients was found to have sickle cell anemia. No patient had any blood dyscrasia.

TABLE 1 *Summary of cases: Undiagnosed, gross renal bleeding*

CASE NO	AGE YRS	SEX	RACE*	BLEEDING KIDNEY	HISTORY OF HEMATURIA†	TREATMENT	LENGTH OF FOLLOW UP†	FINAL RESULT
1 J R	17	M	N	L	10 d	Nephrectomy	6 y	No further bleeding
2 W W	54	M	W	Both	31 y	L nephrect 12 yrs before	6 y	R kidney bleeding
3 J W de H	44	M	W	L	9 y	AgNO3 lavage renal pelvis, P R N	5 y	Occas L kidney bleeding
4 G A S	55	M	W	R	6 m	Transfusions, finally nephrect	4½ y	No further bleeding
5 J M B	17	F	N	R	2 w	None	4½ y	Prompt cessation
6 W N J	36	M	W	L	19 y	None	4½ y	Hemat ceased
7 N W	35	F	N	R	2 d	None	4 y	Hemat ceased
8 B S	21	M	N	L	4 m	Transfusions, finally nephrect	4 y	No further bleeding
9 L B	47	F	N	L	2 m	None	3½ y	Hemat ceased
10 M C P	31	F	W	R	3 d	Vitamins C, K, transfusions	3 y	No further bleeding
11 S J D	38	M	W	R	2 d	? Total dental extraction	3 y	No further bleeding
12 C C S	66	M	W	L	5 d	None	3 y	Hemat ceased
13 P W	37	M	W	R	4 m	? Tonsillectomy	2 y	No further bleeding
14 O G P	34	M	W	L	3 d	None	2 y	Hemat ceased
15 A B P	19	F	N	R	2 w	None	18 m	Hemat ceased
16 J D	38	M	N	L	2 w	? Tumor→explor→nephrectomy	10 m	No further bleeding
17 J M	23	M	N	L	1 m	Profuse, irreg blood loss, → nephrectomy	10 m	No further bleeding
18 H F	43	F	W	R	9 m	None	6 m	Hemat ceased
19 D W	57	M	W	R	4 y	None	6 m	Hemat ceased

* N—Negro, W—White

† d—days, w—weeks, m—months, y—years

of bleeding from each kidney was found, and in 1 instance, bilateral bleeding occurred In the latter case, right renal bleeding began shortly after a left nephrectomy, and was observed cystoscopically when the patient first came to us for study, 12 years after surgery

Conservative treatment consisted of all the nonoperative methods commonly employed, including use of vitamins C and K, cobra venom, cortisone, blood transfusions and lavage of the affected renal pelvis with silver nitrate solution These appeared at best to be only palliative In most cases, unless profuse renal blood loss was manifest, a policy of watchful waiting was adopted Frequent pyelographic examinations were made, at about 3-month intervals or more often, when indicated That this policy was worthwhile in the preservation of renal tissue was indicated by the spontaneous cessation of the hematuria in 9 cases. In 2 cases, intermittent, moderate hematuria persisted.

A total of 5 nephrectomies was performed by us. In one situation (case 16) early tumor was strongly suspected preoperatively, and at surgery an indurated area was palpated in the lower pole of the kidney. Only dilated vessels within otherwise normal parenchyma were observed microscopically. In 2 instances, the renal bleeding was excessive and was uncompensated by blood transfusions (cases 4 and 8). In another patient the blood loss was massive and nephrectomy proved to be an emergent, life-saving procedure (case 1). Interestingly enough, in 1 case, blood transfusions and vitamin therapy sufficed to tide the patient over her phase of acute bleeding; the hematuria ceased spontaneously and permanently within 2 months (case 10).

Only conjecture can be made as to the possible existence of "focal infection" as a cause of renal bleeding. Two of our patients achieved complete and prolonged termination of renal bleeding after dental extraction and relief of pyorrhea (case 11), and tonsillectomy (case 13). At the time of the most recent examination, no recurrence of the bleeding could be found in either patient.

All follow-up studies, consisting minimally of physical examination, cystoscopy with retrograde pyelography and microscopic analysis of the catheterized urine from each kidney and the bladder, were performed within 3 months prior to the writing of this report.

Figure 1 illustrates typical pyelographic studies, revealing absence of any radiographically identifiable lesion that might explain the hematuria.

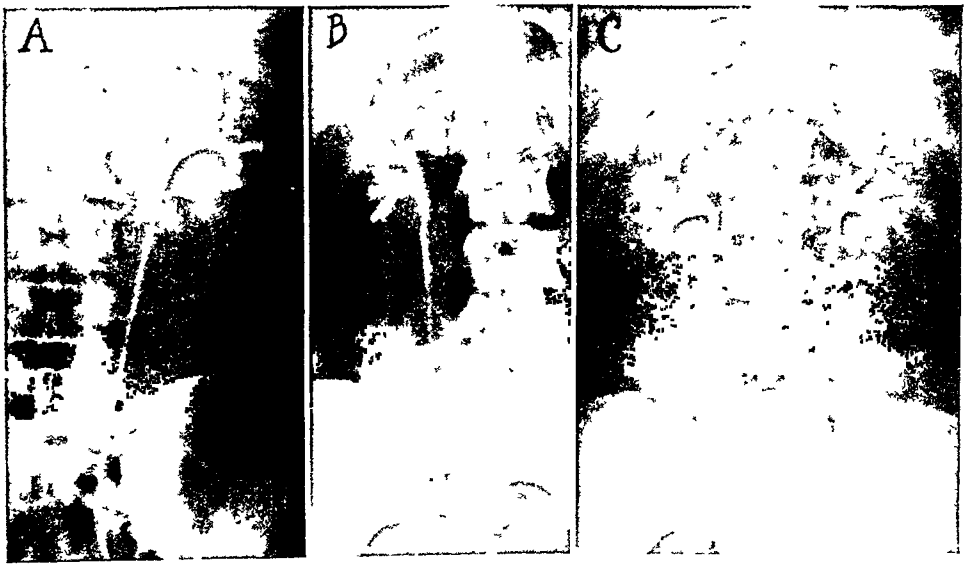

Fig. 1. *A*, case 3. Bleeding from left kidney began 1946. Constant bleeding except for short time after $AgNO_3$ lavages of renal pelvis. Unchanged pyelogram 3 years later is reproduced. *B*, case 10. Severe right bleeding began in 1950 and stopped 2 months after blood transfusions and massive vitamin C and K therapy in hospital. No recurrence by 1953, as depicted. *C*, case 15 Painless bleeding of 2 weeks' duration in 1951, ceasing spontaneously after 2 months. Baby delivered normally in 1952. No recurrence of hematuria and patient again pregnant by February 1953.

DISCUSSION

The variety of titles assigned to undiagnosed renal bleeding attests, per se, to our ignorance of this process. Among these appellations are "essential hematuria,"[15] "idiopathic hematuria,"[16] "primary renal purpura,"[17-19] "chronic hemorrhagic papillitis,"[20-22] and, most recently, "palindromic renal purpura,"[13] to cite but a few. Fundamentally, the single purpose of all authors should be to classify these phenomena so that consistent diagnostic and therapeutic considerations may be applied in lieu of better knowledge at present of this type of renal bleeding.

In none of the specimens of the kidneys removed in the present series could eosinophiles be found in sufficient quantity to excite comment. Thus the report of Nation et al.[13] could not be corroborated here. The "chronic inflammatory and vascular changes in the papillae" described in some of Cahill's cases[23] were not characteristically nor commonly observed in our specimens. In brief, the histological pictures showed very little change, if any, as compared with normal, postmortem specimens of healthy adults.

Higgins contended that hematuria "if only on one occasion, means the presence of organic disease."[24] So broad a statement must be challenged in view of the spontaneous cessation of hematuria in almost 50 per cent of the patients reported in the present review. An organic cause would by definition necessarily suggest intrarenal changes beyond physiological alteration or ready reversibility. Conceding our clinical and laboratory limitations in detecting minute changes in a given patient's bodily economy, it is still perplexing that hematuria, often of many years' duration, should suddenly be relieved without features discernible to the physician. In any case, the self-limitation of this renal bleeding, in the absence of therapy, hardly signifies any known, severe organic disease.

In support of our argument, two revealing cases of prolonged, "nonorganic" hematuria may be excerpted from the many included in table 1. One patient (case 6) experienced persistent unilateral renal bleeding for 19 years; this ceased spontaneously and has not recurred during the past 4½ years. Another (case 3) has had benign, intermittent blood loss from one kidney for 9 years without ill-effect.

From a practical viewpoint, therapy must be arranged in accordance with the magnitude of the blood loss in the particular patient. If persistent, protracted bleeding does not adversely affect health, it may be assumed that compensatory mechanisms (increased erythropoiesis, etc.) are adequate to combat

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[22] MacGowan, G J Urol , 9: 331–343, 1923

[23] Cahill, G F J Urol , 47: 224–234, 1942

[24] Higgins, C C Cleveland Clin Quart , 17: 160–165, 1950

the disorder. Conservative management is urged. Temporization does no further harm, provided that the patient is carefully and judiciously followed. Avoidance of pre-emptory ablation of a bleeding kidney may well prevent the distressing situation wherein unexplained and possibly uncontrollable hemorrhage from a remaining kidney develops later. In two of our cases the patients refused surgery, which would most likely have been nephrectomy. Subsequently, these individuals enjoyed spontaneous remission without recurrence of renal bleeding for over 5 years.

In addition to the 18 cases of undiagnosed renal bleeding, without pyelographic deformity, cited by McKay et al. in 1949,[16] about 11 other similar cases have been subsequently reported.[13, 14, 15, 19] Thus, the present study constitutes the largest single group of cases of undiagnosed, gross renal bleeding which has come to our attention.

SUMMARY

Nineteen cases of unexplained, gross renal bleeding have been presented. Most were males under 45 years of age. Complete urological studies were ineffective in identifying the cause or renal site of the hematuria. Nine patients enjoyed spontaneous and seemingly complete remission without treatment. Two others were relieved apparently following eradication of "focal infection". Five nephrectomies were performed because of profuse bleeding or suspected tumor. In none of the surgical specimens could histopathology be demonstrated to explain adequately the renal bleeding observed clinically.

No method of improved diagnostic facility was found. Conservatism, in order to avoid hasty nephrectomy, was recommended.

ADDENDUM

Since submitting our paper for publication, a report of 8 cases of unilateral renal bleeding of which 6 were controlled by vitamin K therapy has appeared (Strasberg, A. and Courteau, R.: "Essential Hematuria", Canad. Med. Assn. J., **68**: 253–255 1953). The vitamin was administered either during relatively brief hospitalization or by a "course of vitamin K". The Canadian authors suggested that " . . . prothrombin deficiencies will explain more and more of these cases of so-called 'essential hematuria' and that fewer nephrectomies will be the rule."

While we strongly support the goal of judicious conservation of normal kidneys, our experience does not coincide with that of Strasburg and Courteau either as to etiology or response to vitamin K therapy. Indeed, recurrence of bleeding, and even *de novo* hematuria from a remaining kidney, has been encountered during massive vitamin K therapy.

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ANEURYSM OF THE RENAL ARTERY

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About one week before admission to the hospital on November 21, 1952, a 67 year old white woman experienced a slow onset of a dull ache in the low back region present daily with no preponderance as to side until the day of admission when it became more pronounced on the left with radiation around to the anterior abdomen and down the left thigh. There were no bladder signs or symptoms and no history of recent or old injury. In the past several years she had had intermittent, recurrent attacks of low backache which were not particularly disabling and not localized to one side exclusively. In 1947 the first attack of pain was associated with nausea and vomiting, but physical and laboratory examinations were nonrevealing. She was again seen by her physician in 1950 for a recurrence of the pain which responded to medication. The remainder of the past history is not contributory to this illness.

Physical examination revealed a somewhat obese white woman who was apparently not acutely or chronically ill. The blood pressure was 220/160. Neither kidney was palpable or tender and the abdomen revealed no masses, tenderness, or rigidity. All laboratory studies were within normal limits. Excretory urography and retrograde pyelography revealed normal structure and function of the kidneys and ureters. However, a radiopaque, annular shadow measuring 15 mm. diameter was located in the hilum of the left kidney slightly inferior and anterior to a very small renal pelvis. The shadow was incomplete in its superior portion and had a relatively radiolucent center. These radiographic findings were strongly suggestive of an aneurysm of the renal artery or one of its branches (fig. 1, *A* and *B*).

Under general anesthesia the kidney was exposed by the usual left lumbar approach. By careful dissection the renal vessels were isolated and stripped of adherent fat following which a chromic tie was placed around the pedicle. Distal to this a transfixation ligature was placed, the ureter was cut between chromic ties, and the kidney removed. A few seconds later considerable bleeding was seen coming from the region of the renal vessels which were then grasped with a curved Kelly hemostat which stopped the bleeding. A third chromic ligature was secured beyond the tip of the clamp. Because of the possibility of there being some inherent weakness of the vessel walls it was decided to leave the clamp in place and close the wound around it. This was done and the patient returned to her room in very good condition. There were no significant blood pressure changes noted during the operation.

The surgical specimen was examined several days after alternate freezing and thawing during the photographing of it, consequently the histological sections were too poor for accurate study. The kidney weighed 116 gm. and was quite soft and flabby. The capsule stripped easily leaving a smooth surface. The attached renal artery was deformed by a 15 mm. diameter spherical dilatation which was stony hard and located in the renal hilum (fig. 2, *A* and *B*). On section-

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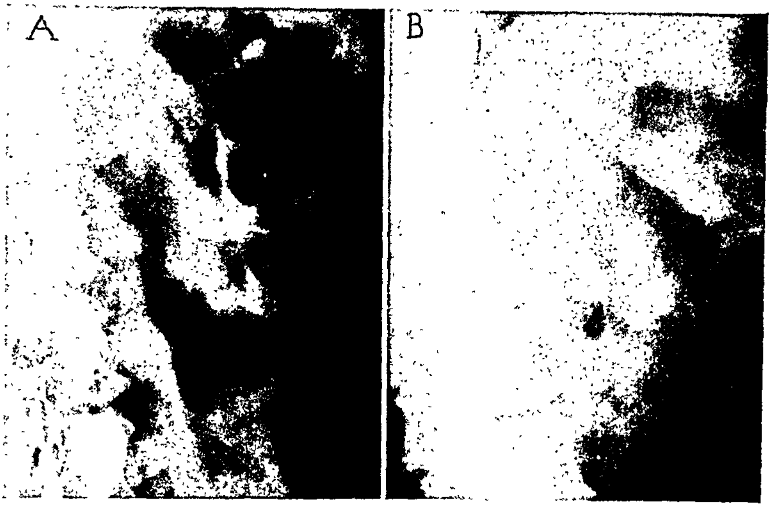

FIG. 1

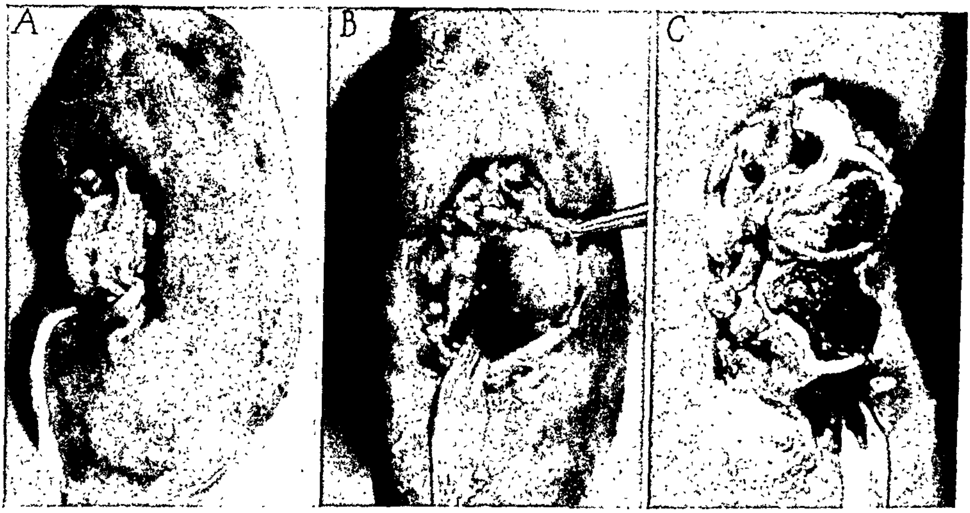

FIG. 2

ing the dilated area the knife was met with marked resistance due to the calcification of the walls which measured about 2 mm. in thickness. The lumen of the aneurysm was filled with brown-black, old hemorrhagic debris (fig. 2, *C*). Cut section of the kidney revealed fairly distinct markings.

On the fifth postoperative day the pedicle clamp was removed and the patient was discharged on the tenth day. About three months postoperative the blood pressure had remained at 180/110.

DISCUSSION

Aneurysms are classified as true and false. A true aneurysm is an outpouching of the vessel which is formed by one or more coats of the vessel. A false aneurysm is actually not an aneurysm but is a walled-off hematoma resulting from rupture of a normal vessel or of a true aneurysm. The incidence of true aneurysms is very low, there being only 80 cases reported. The latest survey of the literature was done by Abeshouse in 1951.[1] He reported a total of 115 aneurysms of which

[1] Abeshouse, B. S.: Urol. & Cutan. Rev., 55: 451–463, 1951.

35 were false Because false aneurysms are merely wall-off hematomas and resemble true aneurysms only because of their limitations by anatomical barriers, their inclusion in any statistical survey is not justified and serves only to confuse the real incidence of true aneurysms

The etiology is unsettled and debatable but the following points might be mentioned

1) *Inflammation* producing a weak area in the arterial wall is probably not important because only 1 of 80 cases reported had syphilis and there was only one case each of rheumatic endarteritis and tuberculosis

2) *Congenital causes* such as a developmental defect in the elastic tissue and media have been suggested but no definite proof has been offered

3) *Degeneration* such as arteriosclerosis plays an important part as seen in the finding of 12 such lesions in a series of 75 cases of both true and false aneurysms of the renal artery reported by Lowsley and Cannon

4) *Trauma*, in the past, has been over-emphasised as a cause of these aneurysms Mathé[2] reported a history of trauma in 23 of 55 cases, and Lowsley and Cannon[3] reported an incidence of 33 per cent of their 75 cases However, trauma probably is an important factor only after the artery has been weakened by disease

Hypertension has been reported in some of the cases as being related to the aneurysm and in others no definite relationship could be established Furthermore, several cases of associated hypertension were relieved by nephrectomy but many others were not significantly benefited

The prognosis varies with the treatment In Abeshouse's series of 115 cases of both true and false renal artery aneurysms 31 per cent were not operated upon and were dead within a variable period of time not greater than 5 years Various "conservative" operations such as partial excision of the aneurysm, exploratory operation, incision and drainage of a false aneurysm, denervation of the renal pedicle, kidney decapsulation and separation of the kidney from the aneurysm by division of adhesions resulted in a mortality rate of 53 per cent On the other hand, nephrectomy produced a mortality rate of 6 per cent in 53 cases

Treatment of renal artery aneurysms is generally regarded to be nephrectomy by most urologists When the diagnosis has been made or suspected nephrectomy is mandatory rather than merely advisable It is redundant to say that rupture of an aneurysm demands immediate operation Conservative operations are applicable in very few cases, Mathé has successfully excised an aneurysmal sac accidentally discovered during sympathectomy

SUMMARY

Aneurysms of the renal artery are quite rare and few reports are to be found in the literature The exact number of cases of true aneurysm is difficult to determine because of the inclusion of cases of so called false aneurysms The mortality rate is low following nephrectomy as compared with nonsurgical or conservative treatment

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[3] Lowsley, O S and Cannon, E M J A M A , 121: 1137, 1943

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THROMBOSIS OF THE INFERIOR VENA CAVA AND RENAL VEINS WITH HEMORRHAGIC RENAL INFARCTION

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Hemorrhagic infarction of the kidneys due to thrombosis of the inferior vena cava and renal veins is an extremely rare entity as opposed to hemorrhagic renal infarction resulting from localized renal vein thrombosis. The literature is relatively abundant with reference to localized renal vein thrombosis[1, 2, 3, 4, 5] and to date, four such cases[4, 6] have been correctly diagnosed and nephrectomy performed, the most recent having been reported by Milburn.[7]

Weber and his co-workers[8] have reported 10 cases of thrombosis of the inferior vena cava occurring in adults varying in age from 28 to 62 years. Derow and his associates[9] reported one case occurring in a 15 year old boy and Lutembacher[10] reported a case of gradual obliteration of the inferior vena cava beginning at the age of 16 in which the patient survived 15 years. Most recently, Feriozi et al.[11] presented a case of thrombosis of the inferior vena cava and renal veins with hemorrhagic renal infarction occurring in a 4 month-old infant.

It is the purpose of this paper to present a case of extensive venous thrombosis including the femoral and iliac veins, the inferior vena cava and the renal and suprarenal veins associated with bilateral hemorrhagic renal infarction occurring in a 19 month-old female infant. Review of the literature fails to disclose a case of such extensive involvement occurring in infancy.

CASE REPORT

A 19 month old white girl was admitted to the Binghamton City Hospital on June 7, 1952 with the complaints of vomiting, diarrhea and gross hematuria. History revealed that on May 5, 1952, an afebrile illness developed characterized by severe vomiting and an excoriating diarrhea which gradually improved in about 3 days under conventional therapy with kaopectate and paregoric. In retrospect, the interval history was significant in the fact that the child appeared to experience lumbar pain on being picked up and also that she was reluctant to walk. On the day of admission, vomiting and diarrhea recurred and she passed a large amount of grossly bloody urine containing some clots.

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[3] Morison, J. E.: Arch. Dis. Childhood, **20:** 129–134, 1945.

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[7] Milburn, C. L.: J. Pediat., **41:** 133–140, 1952.

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[10] Lutembacher, R.: Presse méd., **43:** 1175, 1935.

[11] Feriozi, D., Rice, E. C., Burdick, W. F. and Troendle, F. J.: J. Pediat., **38:** 235–241, 1952.

Physical examination on admission revealed an acutely ill, lethargic, moderately dehydrated infant with profound pallor of the skin and mucous membranes The rectal temperature was 103 2F, the blood pressure 122/60 and the pulse 120 per minute The remainder of the significant physical findings were limited to the abdomen where the superficial veins were markedly dilated and the abdomen was distended There was tenderness to pressure and rebound tenderness throughout the entire abdomen and no peristalsis could be heard A firm, tender, smooth, immovable, crescent-shaped mass was palpable in the left para-umbilical region Catheterization obtained only a few cubic centimeters of bloody urine and rectal examination revealed light yellow feces on the examining finger

The erythrocyte count was 2 25 million per cubic mm , hemoglobin 3 75 gm with a color index of 0 51 The leukocyte count was 10,000 per cubic mm with a differential count of 21 per cent lymphocytes, 1 per cent basophils, 2 per cent stabs and 76 per cent segmented polymorphonuclear leukocytes The nonprotein nitrogen was 134 5 mg per cent An abdominal flat film showed no free air under the diaphragm and gas was seen in the large and small intestine but no unusual pattern or distribution was noted A barium enema was considered as essentially normal and a chest film revealed only slight cardiac enlargement in the transverse diameter

The infant was treated supportively and given daily whole blood transfusions of 150 cc each on the first 3 days, fluids of glucose, saline and Ringer's solution, penicillin and vitamin K daily parenterally A cut down was performed in the left ankle to facilitate intravenous therapy During the first 24 hours following admission, the superficial abdominal vein dilatation and the abdominal distention subsided but both subsequently recurred Two days after admission, bilateral ankle edema was noted, intravenous therapy was stopped for 24 hours and the cut down in the left ankle was discontinued Three days after admission, cystoscopy and retrograde urography were done under ether anesthesia At that time, although no urine was seen to enter the bladder, the lower urinary tract and retrograde urograms were considered normal Abdominal examination under anesthesia revealed the previously described abdominal mass to be about four inches long and located just beneath the left costal margin in the midclavicular line The red cell count had risen following the transfusions to 3 53 million with a hemoglobin of 9 gm while the white cell count had risen to 17,900 On the third hospital day, the nonprotein nitrogen was reported as 91 5 mg per cent and the blood chlorides as 425 mg per cent Following cystoscopy, intestinal intubation and hourly gastric lavage with tap water was instituted and 3 days after admission, the temperature had fallen to normal The infant had only an occasional loose bowel movement and urination consisted of slight diaper saturation staining the diaper pink The blood pressure ranged between 90 and 100 mm of Hg systolic and 60 and 70 mm of Hg diastolic Five days after admission, the serum sodium was reported as 203 8 mg per cent, the serum potassium as 18 95 mg per cent, the blood chlorides as 380 mg per cent and the nonprotein nitrogen as 104 mg per cent

The general condition of the patient had improved so that gastric lavage was discontinued on the sixth hospital day and she was able to retain fluids and soft foods. Despite the fact that she received only 300 to 900 cc of fluid a day, the urinary output improved somewhat but the diapers continued to be stained a light pink. Loose bowel movements had now ceased and the stools were soft but formed, varying in color from light yellow to dark brown and, except for one or two occasions, the vomiting had ceased. The first measureable amount of urine obtained eight days after admission revealed an insufficient quantity for specific gravity, a light greenish-amber color, an alkaline reaction, albumin 75 mg. per cent, 10 to 15 white blood cells per high power field, a few motile bacteria and amorphous phosphate crystals; no red blood cells or casts were seen. The nonprotein nitrogen at that time had risen to 145 mg. per cent and the blood chlorides were reported as 440 mg. per cent.

Two weeks after admission, lethargy and irritability recurred and became progressively worse along with superficial abdominal vein dilatation and abdominal distention despite the fact that the urinary output continued to improve. The nonprotein nitrogen continued to rise and 13 days after admission, it was reported as 193 mg. per cent. Liquid and soft nourishment were now refused and although penicillin therapy had been continued, the cut-down in the left ankle became infected. On June 25, 1952, fine, generalized tremors were noted and intestinal intubation with gastric lavage was re-instituted. The nonprotein nitrogen had risen to 313 mg. per cent and the following day, 20 days after admission, the infant expired following the onset of generalized convulsions.

Postmortem examination: The anatomical diagnoses were—massive acute infarction of the entire left kidney following thrombosis of the renal vein; multiple acute infarctions involving more than two-thirds of the right kidney following thrombosis of the renal vein and its branches; propagated thrombosis of the inferior vena cava superimposed on an organized phlebothrombosis of the femoral veins, the iliac veins and the inferior vena cava with recanalization; multiple recent and old anemic infarctions of both adrenal glands following thrombosis of the adrenal veins.

The postmortem findings of importance, both gross and microscopic, are as follows:

Kidneys: Both kidneys were hard and swollen but the surfaces were smooth. The left kidney was about twice the size of the right kidney and the capsules were thickened, stripping with difficulty. The left kidney weighed 170 gm. and was diffusely reddish-purple in color and on cut section, this color was seen to begin at the papillary portions of the medulla and extend peripherally toward the cortex where there was a narrow zone of pale yellow, swollen cortex remaining. The left renal vein was completely thrombosed with a brownish-purple clot. The right kidney weighed 70 gm. and on cut section, presented a number of discrete, well-demarcated, wedge-shaped areas of pale yellow necrosis in the cortex with some evidence of hemorrhage about these areas. The entire papillary portion of the medulla was a similar pale yellow color. Grossly, the main right renal vein was occluded with thrombotic material and many of the

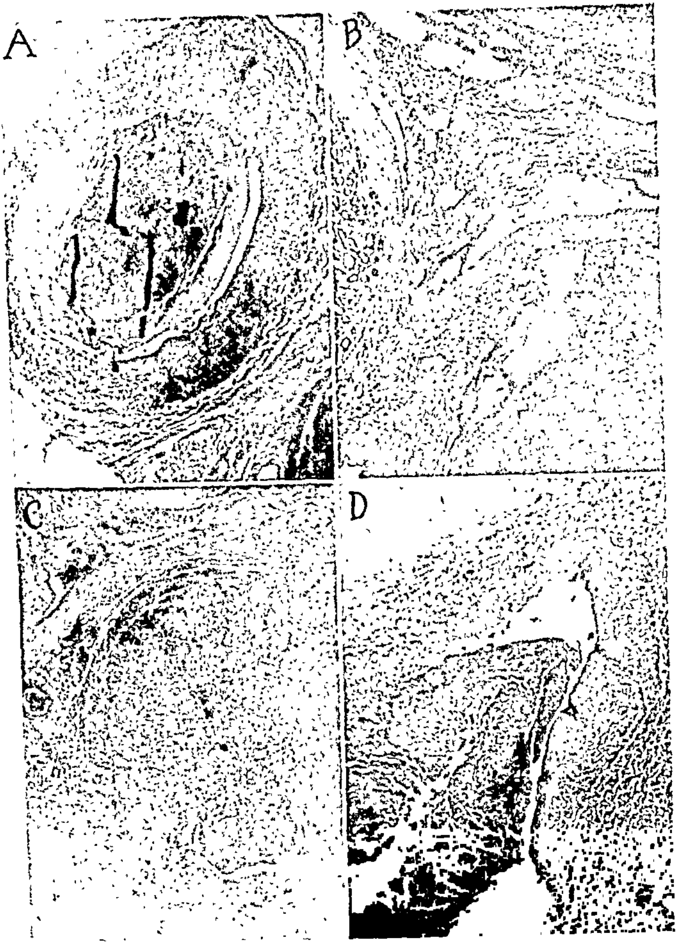

FIG. 1. *A*, low power view of main left renal vein showing complete occlusion by an organizing thrombus. *B*, low power section of right kidney showing partially thrombosed secondary renal vein. Note necrotic kidney tissue in upper right with normal kidney at bottom. *C*, low power view of left adrenal showing thrombotic venous occlusion with surrounding necrosis of medulla extending into portions of cortex. *D*, lower power view of inferior vena cava showing organized thrombus with evidence of recanalization.

secondary veins draining into the renal vein were thrombosed and occluded with old blood clots.

Microscopically, the left kidney revealed a complete, uniform antemortem anemic infarction of the entire kidney substance. Nearly all the renal veins (fig. 1, *A*) were greatly distended with blood clots and the collecting tubules were filled with large amounts of precipitated, granular acidophilic material in which round, deep pink staining albuminous bodies resembling red blood cells were seen. The cytoplasm of the kidney was granular and acidophilic and stained very poorly with complete loss of nuclei staining. The right kidney revealed well-formed glomeruli but the glomerular capillaries were congested and the Bowman's capsules were dilated. The convoluted tubules were greatly distended and the lining epithelial cells showed marked granular degeneration and exfoliation. Only a narrow margin of cytoplasm at the periphery of the epithelial cells was seen to be intact and some of the tubules were noted to be filled with albuminous material. The loops of Henle and the collecting tubules showed marked distention with granular, acidophilic material and the interstitial connective tissue, particularly that of the medullary portion, was edematous with irregular areas of interstitial, polymorphonuclear and mononuclear cell infiltration. Some of the renal veins were thrombosed and completely occluded with blood clots, the portions of renal tissue corresponding to these veins showing complete necrosis (fig. 1, *B*). The cells within this area of necrosis had completely lost their nuclei and were represented by granular, acidophilic material. It was felt that these anemic infarctions were of relatively recent origin.

Adrenals: Grossly, both adrenal glands were well-formed but atrophic and there was no evidence of hemorrhage. Microscopically, the adrenals (fig. 1, *C*) appeared to show two different types of lesions. In the older lesion, the cortex and medulla were completely atrophic and replaced by fibrous tissue while in the more recent lesion, there was evidence of acute adrenal hemorrhage which seemed to radiate from the medullary portion into the remaining viable cortical tissue.

Inferior vena cava: The femoral veins, the iliac veins and the distal two-thirds of the inferior vena cava were thrombosed with evidence of recanalization. Microscopically, approximately three-fourths of the circumference of the inferior vena cava was thrombosed and recanalized (fig. 1, *D*). There was evidence of chronic inflammatory reaction in the surrounding adventitia.

DISCUSSION

Hemorrhagic infarction of the kidney is a very rare disease, usually encountered in the neonatal period, of the most serious magnitude with an extremely poor prognosis for recovery. Kobernick and his associates[5] state that in terms of total necropsies, the incidence of this disease is less than one per cent. A review of the literature[7] indicates that only 258 cases of this disease have been reported and in only four of these has the diagnosis been made clinically and nephrectomy performed with survival of the patient. Approximately one-half of these cases have been unilateral in involvement and there seems to be no predilection for either side or for sex. Bilateral renal involvement is much more serious than unilateral involvement but Fallon[2] has reported a case of bilateral renal vein thrombosis with renal infarction in a newborn infant where the diagnosis was made clinically and in which recovery was spontaneous. When the involvement is unilateral, Campbell and Matthews[6] state that about seventy-five per cent of the patients should be expected to survive when nephrectomy is promptly performed and when sepsis is not marked. It is therefore apparent that the diagnosis should be made as early as possible in the course of the disease so that the patient may be afforded the benefits of surgery.

A definite cause for renal vein thrombosis has yet to be advanced and thus it is in the case which we have just presented. However, a number of predisposing factors have been postulated and Milburn[7] classified these generally as inherent and acquired. Nevertheless, the main etiologic factors have been listed as dehydration, infection, bed rest and possible anatomic factors.[5, 10, 12] In the cases of renal vein thrombosis which have been reported previously, it was felt that the thrombosis originated in one kidney and then extended to the other kidney via the vena cava. In the case which we have presented, an organized and partially recanalized thrombus was found in the femoral veins, the iliac veins and the inferior vena cava. Because of the recanalization evident in the distal portion of the vena cava, the thrombosis can only be explained on an ascending basis. Since the infant had an entirely negative past medical history, it is believed that the original episode of thrombosis occurred when she first became ill approximately one month prior to hospitalization. This would have been an adequate period for organization and recanalization of the thrombus and the involvement of the renal veins was felt to be secondary to the thrombosis in the inferior vena cava and not, as is usually seen, a localized process commencing in the kidneys.

Early diagnosis is complicated by the fact that renal vein thrombosis with hemorrhagic renal infarction is a very rare condition and therefore, the diagnosis may not be entertained by the clinician until the process has so extended that nephrectomy would be valueless. Unless the condition is recognized and nephrectomy performed within a period of time measured in hours or a few days, death will ensue. Death results from uremia, the opposite kidney becoming involved in the thrombotic process by extension of the thrombus to the opposite renal vein via the inferior vena cava or from renal failure resulting from renal insufficiency of the opposite side and/or thrombosis and infarction of the kidney of the involved side.

However, it should be emphasized that renal infarction due to renal vein and inferior vena caval thrombosis is not necessarily limited to the neonatal period as evidenced by the case which has just been presented in which this disease occurred in a 19 month-old female. Previous reference has been made to cases presented by Weber and his co-workers,[8] Derow[9] and to Lutembacher[10] in which renal infarction associated with thrombosis of the renal vein and inferior vena cava occurred in adolescents and adults. Likewise, thrombosis of the renal vein per se is also not limited to the neo natal period. Danhiez[13] and Melick and

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[12] Zuelzer, W. W., Kurnetz, R. and Fallon, R.: Am. J. Dis. Child., 81: 27–38, 1951.

[13] Danhiez, P.: J. d'urol., 23: 481–495, 1927.

(fig. 1, *A*) were greatly distended with blood clots and the collecting tubules were filled with large amounts of precipitated, granular acidophilic material in which round, deep pink staining albuminous bodies resembling red blood cells were seen. The cytoplasm of the kidney was granular and acidophilic and stained very poorly with complete loss of nuclei staining. The right kidney revealed well-formed glomeruli but the glomerular capillaries were congested and the Bowman's capsules were dilated. The convoluted tubules were greatly distended and the lining epithelial cells showed marked granular degeneration and exfoliation. Only a narrow margin of cytoplasm at the periphery of the epithelial cells was seen to be intact and some of the tubules were noted to be filled with albuminous material. The loops of Henle and the collecting tubules showed marked distention with granular, acidophilic material and the interstitial connective tissue, particularly that of the medullary portion, was edematous with irregular areas of interstitial, polymorphonuclear and mononuclear cell infiltration. Some of the renal veins were thrombosed and completely occluded with blood clots, the portions of renal tissue corresponding to these veins showing complete necrosis (fig. 1, *B*). The cells within this area of necrosis had completely lost their nuclei and were represented by granular, acidophilic material. It was felt that these anemic infarctions were of relatively recent origin.

Adrenals: Grossly, both adrenal glands were well-formed but atrophic and there was no evidence of hemorrhage. Microscopically, the adrenals (fig. 1, *C*) appeared to show two different types of lesions. In the older lesion, the cortex *and medulla were completely atrophic and replaced by fibrous tissue while in* the more recent lesion, there was evidence of acute adrenal hemorrhage which seemed to radiate from the medullary portion into the remaining viable cortical tissue.

Inferior vena cava: The femoral veins, the iliac veins and the distal two-thirds of the inferior vena cava were thrombosed with evidence of recanalization. Microscopically, approximately three-fourths of the circumference of the inferior vena cava was thrombosed and recanalized (fig. 1, *D*). There was evidence of chronic inflammatory reaction in the surrounding adventitia.

DISCUSSION

Hemorrhagic infarction of the kidney is a very rare disease, usually encountered in the neonatal period, of the most serious magnitude with an extremely poor prognosis for recovery. Kobernick and his associates[5] state that in terms of total necropsies, the incidence of this disease is less than one per cent. A review of the literature[7] indicates that only 258 cases of this disease have been reported and in only four of these has the diagnosis been made clinically and nephrectomy performed with survival of the patient. Approximately one-half of these cases have been unilateral in involvement and there seems to be no predilection for either side or for sex. Bilateral renal involvement is much more serious than unilateral involvement but Fallon[2] has reported a case of bilateral renal vein thrombosis with renal infarction in a newborn infant where the diagnosis was

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PAINFUL NEPHRECTOMY SCAR

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Painful postoperative scars have been reported as resulting from cutting, traumatizing, or interrupting nerves; or from ligation of nerves along with vessels. A painful fibroneuroma subsequently develops.[1, 2] Moreover postoperative pain has been attributed to adhesions, muscle spasm, and neurosis.[2] It is believed that a further cause of postoperative pain is hereby worthy of presentation.

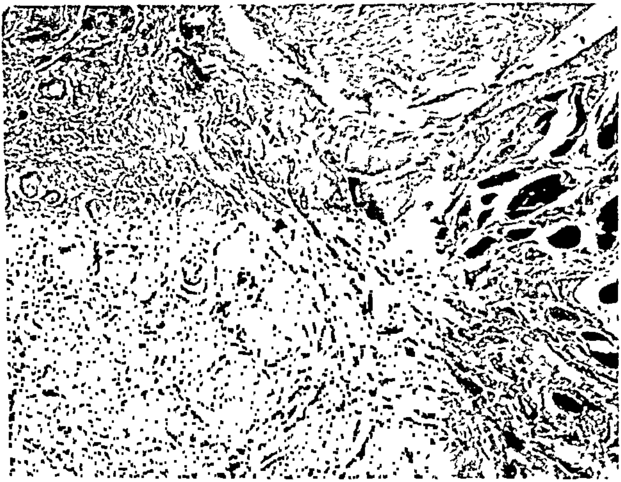

FIG. 1 Hyalinized glomeruli and scar tissue, left; fascia above; and skeletal muscle, right.

CASE REPORT

A 38 year old woman stated that she had always had left back pain even as a child. During her second pregnancy, 9 years before admission, the pain became worse and this was more pronounced after delivery. Subsequent investigation revealed a grade 2 hydronephrosis with marked obstruction at the ureteropelvic junction.

A left nephrectomy was performed on July 1, 1950. The operative note stated: "...A left lumber incision.... While cutting down into Petit's triangle, a cavitation entered which bled profusely. Upon further examination, after ob-

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[1] Bancroft, F. W.: Painful postoperative scars. Arch. Surg., **21**: 293, 1930.

[2] Corbett, J. F.: Painful scars. Minn. Med., **4**: 683, 1921.

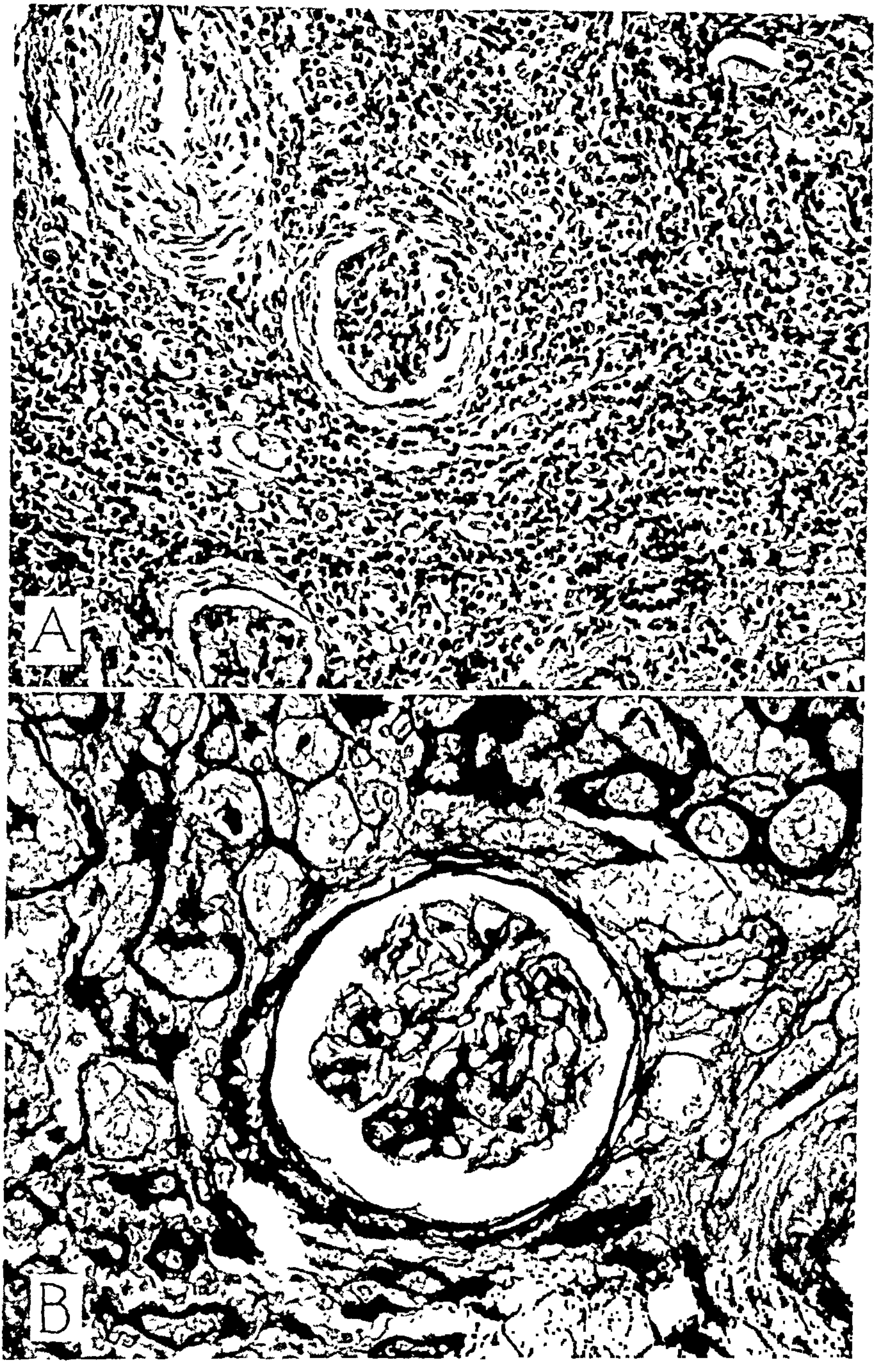

FIG. 2. *A*, kidney tissue showing chronic pyelonephritis and arteriosclerosis. *B*, functioning glomerulus and tubules.

taining access to retroperitoneal space, it was seen that the kidney parenchyma itself was opened into. The kidney was then freed with great difficulty. There was marked scarring and fibrosis completely surrounding kidney. . . ." The pathological diagnosis was chronic pyelonephritis.

Six weeks after the operation she began to complain of needle-like pain in the scar radiating to the left hip, groin and medial aspect of the left thigh. Later the pain changed to a persistent dull one with occasional sharp jabs. The pain was of sufficient severity that she required multiple nerve blocks every 3 weeks and the use of narcotics with but transient alleviation of symptoms. Examination disclosed a left flank scar with tenderness at the junction of middle and dorsal thirds The remainder of the history and physical examination was not remarkable

A second operation was performed 2 years after the nephrectomy (July 31, 1952). The old scar was excised under general anesthesia. Dense fibrous tissue was traced down to the fascia where the fibers seemed to penetrate what appeared to be the old drainage site through the muscle. No nerve was seen.

She was discharged on August 10, 1952 (tenth postoperative day), and was seen in the office on August 29 and November 1 The wound seemed well healed and there was no pain or tenderness.

The pathological specimen exhibited skin, 23 by 1 cm, with subcutaneous tissue, fascia and skeletal muscle 4 cm. deep. In the skin there was a linear scar, while 2 cm below the surface there was an indefinite area of induration 1.5 cm. in diameter. Microscopic examination of the latter demonstrated, amidst fascia and skeletal muscle (fig. 1), functioning kidney tissue with evidence of chronic inflammation (fig. 2). Nerve bundles were seen but no fibroneuroma was encountered

SUMMARY

A case is presented in which a painful postoperative nephrectomy scar is thought to have resulted from a small focus of residual functioning chronically inflammed kidney tissue situated in the deep fascia.

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GIANT HYDRONEPHROSIS; ONE STAGE NEPHRECTOMY

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The problems involved in the management of giant hydronephrosis are well documented in the literature. An excellent and comprehensive review of this subject was presented by Earlam who reported one containing 18 liters of fluid which was nephrectomized in two stages. The differential diagnosis from ascites and ovarian cysts is important, since these abdominal enlargements are produced by fluid. The history obtained from individuals with ascites will usually reveal a prolonged recurrent or progressive disability related to cardiac or hepatic disorders. A woman with an enlarged ovarian cyst or a patient with a giant hydronephrosis may never have been incapacitated, but only concerned with the nuisance of a steadily enlarging abdomen. Shifting dullness and flank distention on recumbency tend to aid in the clinical differentiation of these disorders since encapsulated cysts or a distended renal pelvis usually do not reveal shifting dullness and flank distention on recumbency. The danger in confusing these entities will often lead to trocar drainage, and there is the specific danger of infection from this procedure in giant hydronephrosis.

CASE REPORT

A 72 year old white man was admitted to the hospital in June 1951 with a chief complaint of a "swollen belly." The patient stated that he had noticed progressive enlargement of the abdomen for the past 10 years. He gave no history of pain, except for one episode 2 weeks prior to admission, when he experienced severe abdominal pain which was localized in the left flank and associated with grossly bloody urine. This patient had been unable to work for several years due to the enormous enlargement of the abdomen, although he had not experienced any weakness.

He had always been well and had engaged in farming most of his life. He gave no history of shortness of breath, swelling of the ankles, precordial pain, or jaundice. Three months before hospitalization he was treated at home for pneumonia, from which he recovered promptly. He gave no history of any surgical therapy.

The patient was well nourished. Only the abdominal findings were of significance. There was gross enlargement of the abdomen which measured 45 inches in girth (fig. 1, *A*). It was tense and the costal margin of the ribs flared outward. The abdomen was entirely dull throughout and no peristalsis could be heard. There was no shifting dullness.

The x-rays revealed marked elevation of the left leaf of the diaphragm. Two large calculi were visualized, one of which was a large staghorn stone below the lower pole of the right kidney, and the second was an unusually large round calculus in the lower left ureter (fig. 2, *A*). The excretory urograms showed a normal right renal pelvis with the ureter displaced to the right (fig. 2, *B*). No

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The material in the paper formed the basis of a scientific exhibit at the annual meeting, American Urological Association, Atlantic City, N. J. June 23–26, 1952.

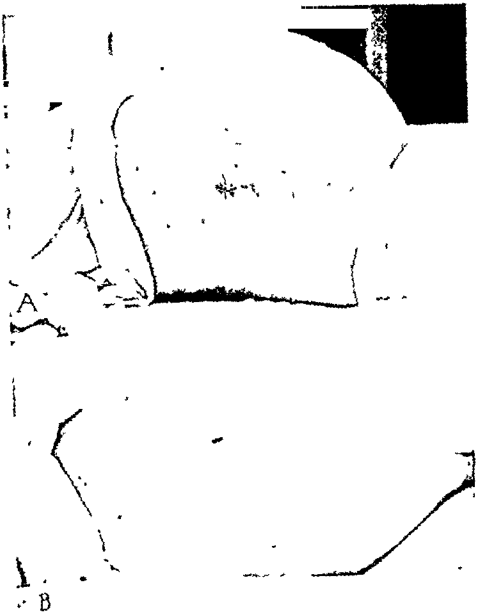

FIG. 1. A, patient on operating table. Waist measurement 15 inches. B, postoperative waist measurement 36 inches

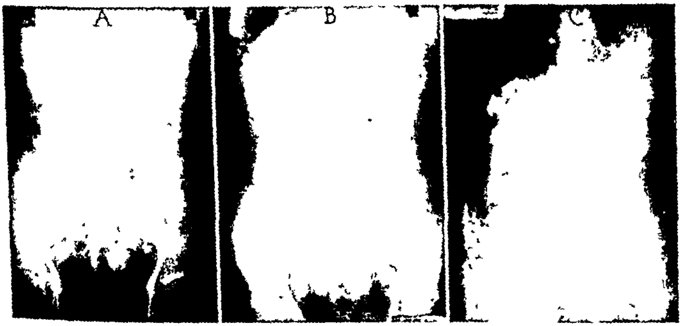

FIG 2 A, plain x-ray reveals staghorn calculus below right kidney, and large, round stone in lower left ureteral region B, excretory urogram shows normal right renal pelvis with ureter displaced to right No dye visualized in left renal area C, upper gastro intestinal series shows small intestines displaced to right side of abdomen

excretory dye was visualized in the left renal pelvis The stomach and small intestines were displaced to the right (fig 2, C). The transverse colon was displaced upward, while the descending and sigmoid colon appeared to be displaced to the left.

During the cystoscopic examination the left ureter could not be catheterized beyond the intramural portion.

The operation consisted of a one stage nephrectomy using endotracheal anesthesia. A cutaneous ureterostomy was done through a left flank incision. Ten liters of old blood tinged urine were aspirated from the left renal pelvis. There was loss of some fluid when the pelvis was opened. From a separate loculated mass within the renal pelvis an additional two liters of clear amber urine was obtained. The cultures of both specimens were sterile. The staghorn stone was impacted at the left ureteropelvic junction.

The patient's convalescence was prompt and uneventful. He was discharged from the hospital on his twelfth postoperative day (fig. 1, *B*). The postoperative abdominal girth measurement was 36 inches in comparison to 45 inches preoperatively. Slight drainage occurred from the cutaneous ureterostomy for 3 months, followed by firm healing.

SUMMARY

A giant hydronephrosis of 12 liters is reported in a 72 year old white man. The diagnosis was made preoperatively. Following the one stage nephrectomy the patient had an uneventful recovery. Differential diagnosis is important as trocar drainage is occasionally performed on these patients resulting in serious complications.

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THORACIC KIDNEY

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A case of congenital thoracic ectopy of the left kidney is described because it represents a rare condition which, while largely asymptomatic, may pose an interesting diagnostic problem.

We have been able to find 10 cases described of congenital thoracic kidney in the available literature. We are reporting this patient making a total of eleven. We also reviewed 2 cases of traumatic herniation of the kidney through the diaphragm, which were symptomatic, and were diagnosed while searching for the cause of chest pain and cough, and costovertebral angle pain. Of the ten reported cases, four were associated with other viscera misplaced into the chest, and only two of these were symptomatic.

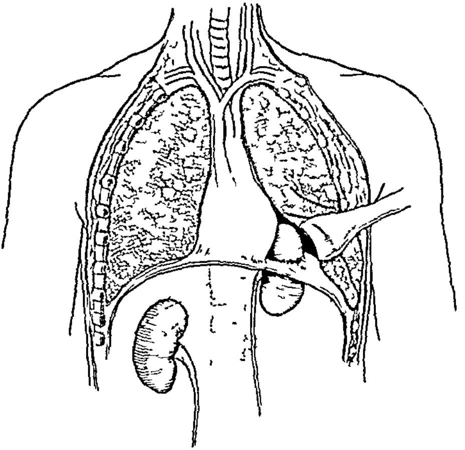

FIG. 1. Left kidney protruding through persistent diaphragmatic foramen.

Renal ectopy is not uncommon. In Campbell's autopsy series, it occurred once in 800 cases, most of which were displaced into or toward the pelvis. Crossed ectopy and medial displacement are occasionally seen, but diaphragmatic herniation with thoracic displacement is decidedly rare. The mechanism of the latter is probably failure of caudal migration of the mesonephros with associated persistence of the diaphragmatic foramen (fig. 1).

A 64 year old Negro was admitted to the urology service with a clinical diagnosis of benign prostatic hypertrophy and early carcinoma of the prostate. He denied present or past symptoms of lung, diaphragmatic, or gastro intestinal

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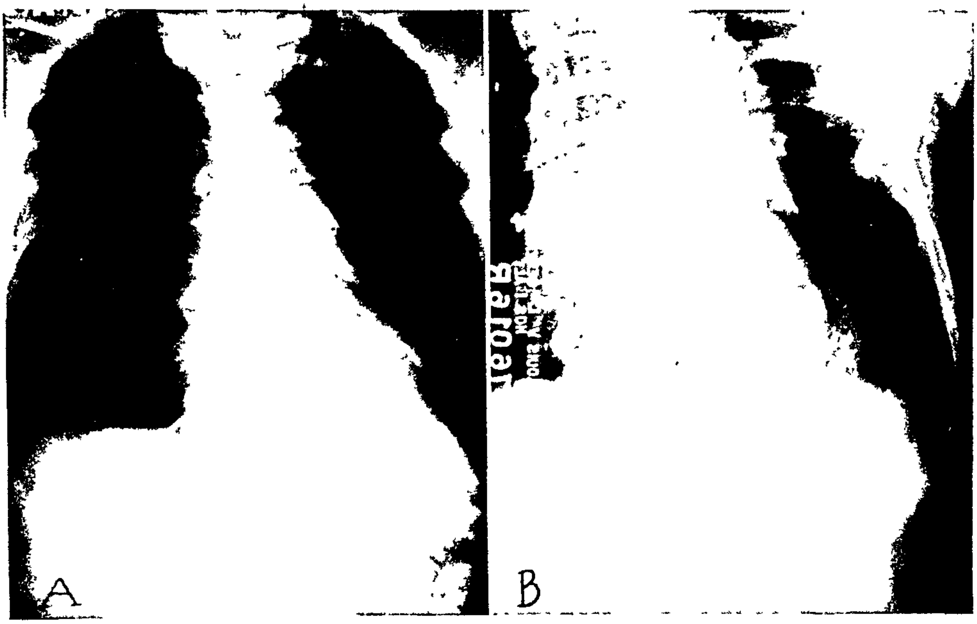

FIG. 2. *A*, admission film showing dome-shaped mass protruding through diaphragm. *B*, retrograde pyelogram, oblique view.

disease. He gave no history of previous accident or operation. The positive physical findings were limited to the prostate gland. The admission chest film showed a dome-shaped mass protruding up from the left diaphragm partially masked by the cardiac shadow, and was thought to represent a tumor of the diaphragm (fig. 2, *A*). Gastro-intestinal examination showed the small and large bowel to occupy normal position. Excretory urography and retrograde pyelography demonstrated the mass to be a morphologically and functionally normal kidney. The upper pole was at the level of the eleventh thoracic vertebra, about 5 cm. above the diaphragm (fig. 2, *B*).

A total retropubic prostatectomy and seminal vesiculectomy was done without incident, the pathologic diagnosis being adenocarcinoma in nodular hyperplasia. No exploration of the kidney was done. The patient has remained asymptomatic for three years without evidence of recurrence or spread of carcinoma.

SUMMARY

A case of asymptomatic congenital herniation of the kidney into the chest is reported. There are ten other recorded instances of this defect, and an additional two cases which were thought to be due to previous trauma.

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PAPILLARY ADENOCARCINOMA OF THE KIDNEY, WITH AORTOGRAPHY RESEMBLING HUGE RENAL CYST

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Aortography has become a widely accepted procedure from the number of arteriograms reported. The chief source of worry in this procedure has been a safe contrast substance which today has been alleviated considerably. The ideal medium should have a low viscosity, low toxicity, extreme x-ray density and be practically nonirritating.[1]

A great disadvantage of arteriography at present has been the limitation of the number of x-ray exposures which is limited to one picture during the injection showing the renal blood flow, and the second just after the injection which outlines the kidney substance (nephrogram). Serial x-rays, with prolonged injection of the ideal medium, will advance the use of this procedure considerably.

VALUES OF ARTERIOGRAPHY

The potential kidney function is in direct relationship to the blood supply of that organ and arteriography offers a visual evaluation of that blood supply. The vascular pattern in normal kidneys is typical, therefore, abnormalities in the arterial pattern are important. It is helpful to the urologist in differentiating avascularity in a space consuming lesion presumably due to a cyst, in contrast to the pooling and puddling of the contrast medium which is supposed to be pathognomonic of tumor.[2] However, we wish to point out that arteriography, despite its usefulness, may occasionally be misleading, as in the case to be presented.

CASE REPORT

A 61 year old white waiter was admitted to McCook Memorial Hospital in September 1952 complaining of pain in the right side of the abdomen of about 1 year's duration. He had also been aware of a fullness and mass in the right side of the abdomen for about one year.

During the 2½ years prior to this admission, he had had 3 admissions to another hospital, each time for severe glossopharyngeal and trigeminal neuralgia, and he had had 3 neurosurgical procedures for the relief of pain. During these admissions, the following significant facts were brought to light. On the first admission, in May 1950, pulmonary tuberculosis was suspected on x-ray, but could not be proven on clinical or laboratory findings, including gastric washings. On the second admission to the other hospital, in March 1951, a large, firm nontender mass was found in the right upper abdomen. Plain x-rays of the

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Read at a meeting of the New England Section, American Urological Association, Hartford, Conn., April 30, 1953.

[1] Melick, J. W., Byrne, J. E. and Boler, T. D.: The experimental and clinical investigation of various media used in translumbar aortography. J. Urol., 67: 1019, 1952.

[2] Doss, A. K.: Referred to by Braasch, W. F. and Emmett, J. L.: Clinical Urography. Philadelphia: W. B. Saunders Co., 1951.

abdomen and barium enema were diagnosed as showing hepatic enlargement and the patient was told he had a fatty liver. The chest x-ray was unchanged. The third admission, for section of the fifth cranial nerve, added no further data.

During the 17 months between the last admission to the other hospital and the present admission to McCook, the following facts were brought to light:

1) He had lost 36 pounds in the past year despite an apparent increase in the size of his abdomen.

2) He had had 3 episodes of hematuria, the last one being 6 months previously.

3) He believed that the abdominal mass itself had increased in size.

4) He had some dyspnea on exertion but no chest pain or ankle edema. Hemoptysis was denied.

In summary then, we have a 61 year old white man who had several operations for trigeminal and glossopharyngeal neuralgia, the last one 17 months previously and apparently very successful. The mass in the abdomen discovered on these hospitalizations was thought to be an enlarged fatty liver, although all liver function studies were normal. During each of these admissions to the other hospital, the urine showed 1 plus albumin, 1 plus white blood cells and 1 plus red blood cells, but no other genito-urinary studies were done except a nonprotein nitrogen determination which was always normal.

The patient was referred now to the McCook Memorial Hospital by a physician who was seeing him for the first time, his impression being "carcinoma of the colon with metastases to the liver." When seen in the admitting room at McCook, he was referred to the urology service because of the episodes of gross hematuria and the ballotable mass in the flank. The attending surgeon and resident who saw the patient felt that the mass was most likely kidney.

Physical examination showed a well developed man of 61 who did not appear to be acutely ill. Vital signs were normal and the head and neck, heart and lungs were normal. There was no adenopathy and no loin tenderness. There was a huge mass in the right side of the abdomen extending from the costal margin to the anterior superior iliac spine and across the midline to about 2 inches to the left of the midline. The mass was ballotable in the flank, was about the size of a large honeydew melon, very smooth and resilient.

The genitalia were normal. Rectal examination showed a 2 plus benign prostatic enlargement. The extremities and nervous system were intact grossly.

The impression on the admission examination was cyst or hydronephrosis of the right kidney—this was chiefly because the mass felt like a cavity containing fluid.

Laboratory data showed 1 plus albumin, 2 plus white blood cells, and microscopic hematuria. The hematocrit was 37 and the remainder of the hemogram was normal. Sedimentation rate was 38 mm/hr. The nonprotein nitrogen was 36 mg. per cent. Total proteins were normal. Feces were negative for occult blood. Bleeding and clotting time were normal and prothrombin time was 50 per cent.

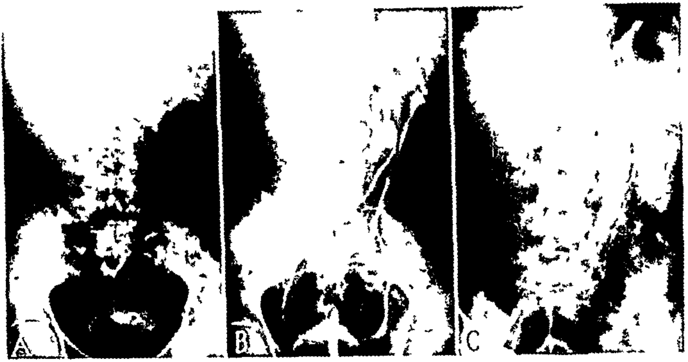

Fig. 1. A, excretory urogram showing mass in right side of abdomen with nonfunctioning right kidney. B, retrograde pyelogram showing distortion of right renal pelvis and calyces with medial displacement of right ureter. C, aortogram obtained by translumbar aortography showing displacement of aorta and paucity of vessels in right renal mass.

The x-rays were very interesting. The chest x-ray on admission showed an arteriosclerotic aorta and bilateral apical tuberculosis, fibrosed, and considered inactive or healed.

The excretory urogram showed a normal left kidney, but no function was discernible on the right. The right side of the abdomen was the site of a large opaque density corresponding to the abdominal mass felt on physical examination (fig. 1, A).

The retrograde studies showed obvious medial displacement of the upper right ureter and distortion of the right renal pelvis and calyces. The left kidney again appeared normal (fig. 1, B).

Aortography had to be done three different times before satisfactory films were obtained. The first one was done on a Friday, and the dye was seen to be outside the aorta. The next was done the following Monday and showed an excellent filling of the celiac axis, especially the splenic artery, so aortography was repeated two days later and what were felt to be excellent diagnostic films were finally obtained. These films were thought to be rather typical of a large renal cyst. The aorta was displaced far to the left and this may be the explanation for the difficulty in obtaining satisfactory films the first two times (fig. 1, C).

Presacral oxygen insufflation after the method of Ruiz Rivas was done prior to the first aortography but none of the oxygen ever dissected its way around the right renal mass. (We have found, as have others,[3] that large retroperitoneal masses seal off the retroperitoneal fascial planes, thus preventing the diffusion of oxygen around them.) This procedure caused the patient considerable abdominal and back pain and was not repeated. The preoperative diagnosis was "huge cyst of the right kidney with medial displacement of the kidney and ureter and no function of this kidney."

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[3] Campbell, M. F.: Pediatric Urology. Philadelphia, W. B. Saunders Co., 1951.

Operation: The patient was in the left lateral decubitus position and the usual kidney incision was made. The presenting portion of the mass was exposed extraperitoneally without any difficulty and was smooth and cystic to palpation. It had a thick capsule, green in color. A trocar was inserted, and only about 450 cc of dark brownish fluid could be aspirated. The cyst would not collapse. It was felt that it might be multiloculated and so it was opened between guy sutures. The interior was filled with a large amount of greenish crumbly material something like dry oatmeal. No more fluid was visible.

Since the cyst would not collapse by aspiration, it was decided to remove it in toto, together with the nonfunctioning kidney. The twelfth rib was therefore resected without incident and the mass was freed by sharp and blunt dissection. Bleeding was moderate and was controlled with hot packs. When the mass was finally shelled out, the ureter having previously been ligated and sectioned, it was seen that the kidney was lying in its bed, split wide open as a book would be opened in the middle, and still attached to the renal pedicle.

The split open kidney was bleeding moderately, and this was easily controlled by manual compression of the pedicle. The pedicle was then clamped, cut, and suture-ligated, the kidney being removed without difficulty. After a Gelfoam sponge had been placed at the site of the upper pole and right adrenal gland where there was some oozing, two Penrose drains were inserted and the wound closed in layers. The patient received 1500 cc blood during and immediately after the operation and was returned to the ward in satisfactory condition.

Pathologic report (Perry Hough, M.D.): The specimen consisted of a glob-

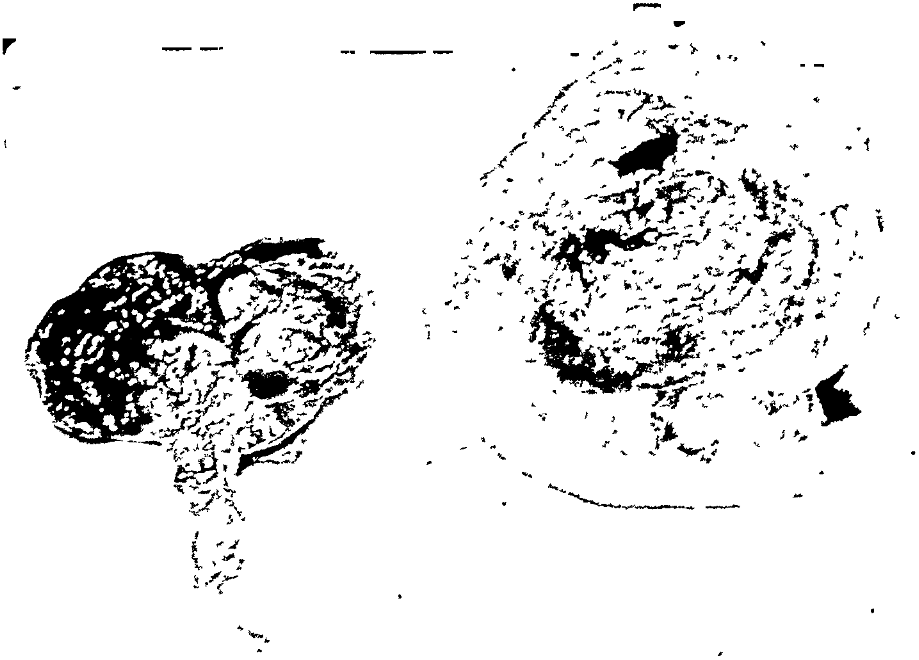

FIG. 2. Gross specimen tumor, and kidney split open from pole to pole in delivering what was thought to be huge cyst.

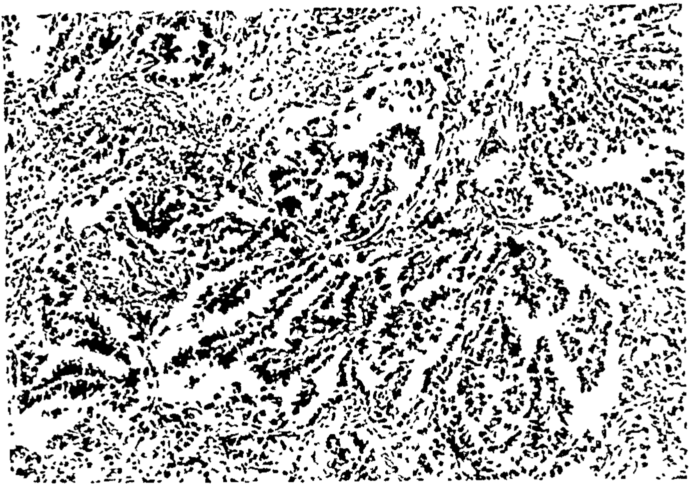

FIG. 3. Microscopic section showing papillary adenocarcinoma

ular, encapsulated, partially collapsed mass of completely necrotic tumor 28 cm. in diameter. The adherent fat was infiltrated by tumor. Separately received was a kidney split open from pole to pole, revealing a hydronephrotic pelvis of moderate degree and attached 8–10 cm. of normal looking ureter. Beneath the pelvic mucosa were found masses of soft grey tumor (fig. 2).

Microscopically the tumor tissue was composed of cuboidal or lower columnar cells forming irregular glandular acini with a papillary arrangement. Anaplasia and mitoses were 2 plus. Areas of necrosis were present. The large central necrotic mass was composed mostly of old blood. Diagnosis: Papillary adenocarcinoma of the kidney, grade 2 (fig. 3).

Postoperative course was uneventful as far as vital signs and wound healing were concerned. The patient had a loose rattling cough, quite persistent, and physical examination showed scattered moist rales bilaterally, but there was no hemoptysis and no chest pain. The sputum was greenish yellow. The patient had a chest x-ray 5 days postoperatively and this showed bilateral pulmonary congestion, an arteriosclerotic aorta, and left ventricular hypertrophy. Because the cough, expectoration and rales persisted, chest x-ray was repeated October 6, 1952 (17 days postoperative) and sputum was sent for acid fast studies. The patient was ready for discharge at this time except for his cough. The chest x-ray now showed, however, extensive infiltration of the left upper and left lower lobes, with fibrotic tuberculous changes in the right upper lobe as well as pneumonitis of the left lung with underlying bronchiectasis. Reactivated tuberculosis was suspected by the roentgenologist. On this same day, sputum was positive for acid fast bacilli, and the patient was transferred to the tuberculosis isolation unit of the hospital where streptomycin and PAS therapy were begun.

Six weeks postoperatively the patient said he was feeling fine, had no urinary symptoms, wound healed completely, cough practically gone and he wanted to go home, but almost every other sputum examination was positive for tuberculosis. He therefore had to follow the tuberculosis regimen of the State of Connecticut and was awaiting transfer to a sanatorium for long term care. Arrangements were made for him to receive radiation therapy to the site of the carcinoma and this was accomplished 6 weeks postoperatively, after which the patient was transferred to the Cedarcrest Sanatorium for treatment of his pulmonary tuberculosis. He finally died of disseminated carcinomatosis in February 1953, at Cedarcrest, proven by autopsy.

SUMMARY AND CONCLUSIONS

A 61 year old white man with a huge mass of the right kidney was subjected to complete urologic investigation, including aortography. A diagnosis of renal cyst was made on the basis of the above workup, especially because of the paucity of blood vessels supplying this mass.

At surgery, the mass was found to be an encapsulated papillary adenocarcinoma of the kidney, grade 2, with adherent fat infiltrated by tumor, as well as tumor beneath the pelvic mucosa.

We believe that because of the extensive and rapid growth of the tumor, massive necrosis and hemorrhage ensued, with lack of blood supply causing renal arteriography to give the appearance of renal cyst rather than neoplasm.

We feel that any patient with an abdominal mass should have excretory and/or retrograde urography to rule out urological disease.

Finally, when there is a space occupying lesion in the kidney, one should still adhere to that time tested phrase, "tumor of the kidney, cyst or neoplasm," and exploration is indicated.

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SPONTANEOUS RUPTURE OF RENAL PELVIS SECONDARY TO A SMALL URETERAL CALCULUS

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Since Wunderlich,[1] in 1856, first described "spontaneous apoplexy of the renal capsule," spontaneous rupture of the kidney has been the subject of clinical reports at irregular intervals. Speese[2] in 1913, and Henline in 1924[3] were able to collect twenty-one and 21 cases respectively. In 1949 Potampa[4] resurveyed the literature and added 2 cases to bring the total to thirty-nine. In addition, the topic has been discussed by Abeshouse,[5] Mathé,[6] Lorenz,[7] and others.

Lowsley and Kirwin[8] state that "some form of renal disease which weakens the walls of the kidney or renal pelvis is a prerequisite to spontaneous rupture," and include as reported causative factors hydronephrosis, lithiasis, tuberculosis, abscess, tumors, and arteriosclerosis. Rupture due to an impacted calculus, however, is exceedingly rare.[9] Abeshouse[5] in his exhaustive article of both traumatic and spontaneous rupture cites nine instances of ureteral calculus and three of impacted stones at the ureteropelvic junction. Salvin,[10] however, in surveying those instances of rupture without trauma secondary to ureteral calculi was able to find but four instances in the literature and added a fifth case.

The occurrence of a case of spontaneous rupture secondary to a small ureteral calculus which was demonstrated by excretory urography, and which was treated conservatively without surgical intervention and with complete recovery of the patient, prompted this report.

CASE REPORT

C. M., U. H. 282-900. A 55 year old white man entered the hospital with the chief complaint of left flank pain radiating to the testicle of 24 hours' duration. The pain was colicky in nature and associated with nausea, but no vomiting. The present illness began at noon of the day prior to admission, when the patient was suddenly seized with severe pain in the left flank. He was seen by his local physician who gave him some morphine with temporary relief, but the pain recurred at irregular intervals until the time of admission. Although there

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[2] Speese, John: Surg., Gynec. & Obst., 16: 571, 1913.

[3] Henline, R. B.: J. A. M. A., 83: 1411, 1924.

[4] Potampa, P. B.: Urol. & Cutan. Rev., 53: 70, 1949.

[5] Abeshouse, B. S.: Surg., Gynec. & Obst., 60: 710, 1935.

[6] Mathé, C. P.: Urol. & Cutan. Rev., 36: 605, 1932.

[7] Lorenz, T. Z.: Urol. & Cutan. Rev., 52: 449, 1948.

[8] Lowsley, O. S. and Kirwin, T. J.: Clinical Urology. Baltimore: Williams and Wilkins, 1944, 2nd ed., vol. 2, p. 1399.

[9] Hinman, F.: The Principles and Practice of Urology. Philadelphia and London: W. B. Saunders, 1936, p. 1008.

[10] Salvin, A. A.: Am. J. Surg., 41: 289, 1938.

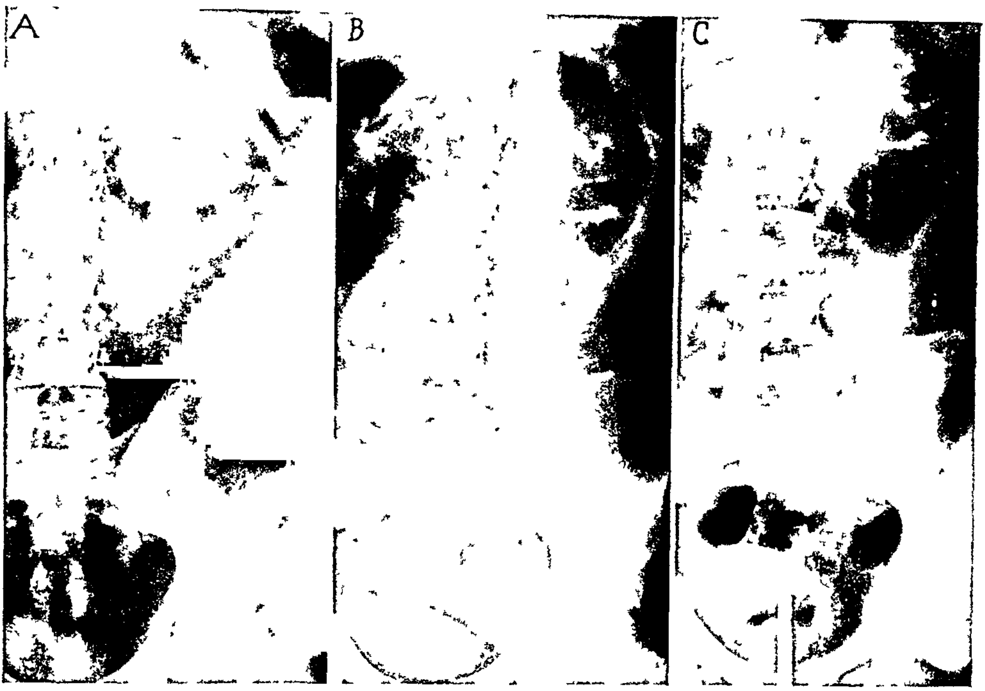

Fig. 1. *A*, plain film showing small calcific density slightly below region of left uretero-pelvic junction. *B*, thirty minute film demonstrating wide extravasation. *C*, retrograde ureteropyelogram made day following excretory urograms showing no evidence of extravasation

was slight dysuria, hematuria was not noted. From the onset of pain the patient was nauseated until admission 24 hours later. Family history and past history were noncontributory. There had been no previous episode of renal colic.

Physical examination revealed a well developed, well nourished male in mild distress. His skin was pale and cool. Temperature was 37.7, pulse 80, respirations 20. Blood pressure was 125/60. Positive physical findings were confined to the back where there was moderate left costovertebral angle tenderness without spasm. There was no abdominal tenderness or spasm. Laboratory data revealed completely clear urine without cells, hemoglobin of 14 grams, and white blood count of 13,200.

The patient had several attacks of colic during the night of admission, which were relieved by narcotics. The plain x-ray (fig. 1, *A*) showed a small calcified shadow suggestive of a calculus in the region of the left ureter below the ureteropelvic junction. The right intravenous pyelograms were completely normal. However, on the left, the intravenous pyelogram, beginning with the ten minute film and increasing up to the 40 minute film, showed definite extravasation of the contrast material (fig. 1, *B*). In a subsequent film taken several hours later, the contrast material had puddled along the psoas shadow.

Following pyelography the patient's temperature, which had previously been normal, rose to 39.5° by 4 p.m. and cystoscopy was undertaken to establish a definite diagnosis and to institute proper drainage of urine if possible. At cystoscopy clear efflux of urine was noted from both ureteral orifices. All attempts to catheterize the left ureter met an obstruction at 1.0 cm. Retrograde injection from this point revealed a normal ureter up to the suspected calculus. The contrast material did not flow past the calculus. The patient was returned to the ward and placed on penicillin. The temperature fell overnight to 38.5°, and the patient had a comfortable night. There was only slight tenderness in the flank. Cystoscopy again was carried out the next morning and it was still impossible to catheterize the left ureter for more than 1.0 cm. Ureteropyelograms, however, were satisfactory and revealed the previously noted shadow to be a small calculus, 2 by 5 mm., just below the ureteropelvic junction. This time the opaque solution flowed beyond the calculus and a normal pyelogram was obtained. No extravasation could be demonstrated (fig. 1, C).

The patient's temperature returned to normal within 24 hours. The leukocyte count fell to 9,800 by the third hospital day. Excretory urography on the sixth hospital day revealed no obstruction, extravasation, or hydronephrosis, and showed only slight descent of the stone. The patient was discharged on the tenth hospital day, and simply kept under observation for 1 month during which time he had no symptoms whatsoever. The excretory urograms were repeated, and again revealed but slight descent of the stone with no obstruction above it. Cystoscopy was also carried out with ureteral catheterization, and no obstruction of the left ureter was demonstrated below the stone.

The patient was re-admitted three, six and nine months after the onset of his illness. He had no urinary symptoms between studies and never any evidence of infection until his last admission when a brief episode of colic preceded his re-entrance into the hospital. Pyelograms, on each occasion, revealed the gradual spontaneous downward passage of the calculus until extraction was possible by means of the Johnson basket, nine months after the initial episode. Retrograde studies at no time showed obstruction, or a distorted pelviocalyceal system. Since removal of the calculus, he has been followed for three years with no evidence of recurrent stone formation, obstruction, or extravasation.

DISCUSSION

Rupture of the kidney occurring without trauma has been categorized by Mathé[11] into two types: a) rupture of the parenchyma with hemorrhage, and b) rupture of the pelvis with extravasation. There is no question of the necessity for surgical intervention in the former case, and the consensus[9, 11] is that it is necessary in the latter instance. However, in this case because of the free efflux of urine from both ureteral orifices, because of the paucity of physical findings and because of the absence of infection it was decided to treat the patient conservatively. The fortunate outcome was indubitably due to several factors, not the least of which was the efficacy of the chemotherapeutic agents employed. If fever or leukocytosis had persisted, ureterolithotomy with drainage would have been employed.

The small size of the stone, an equally important factor in the ultimate fortunate outcome was a determining factor in the program of nonintervention. The failure of the stone to pass immediately, however, was discouraging, and only the repeated retrograde and intravenous pyelograms which showed no extravasation, obstruction, or hydronephrosis, and the patient's extreme reliability and co-operation permitted his temporary discharge and ambulatory observation.

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SUMMARY

A case of spontaneous rupture of the renal pelvis due to an impacted small ureteral calculus, treated conservatively with spontaneous recovery, and with ultimate extraction of the calculus, is reported.

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ACUTE RENAL TRAUMA IN BOXERS

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Professional boxing has been cited as the nation's most dangerous trade.[1] In recent years the attention of the medical profession has been focused upon the boxing industry in an effort to reduce to a minimum the inevitable trauma and the attendant after effects received by its participants.[2]

Brain injuries are the most serious and most dramatic accidents which occur, and the literature is replete with encephalographic studies, for the development of the highly technical instrument and the specialized training necessary for the interpretation of its records have made the detection of brain trauma a feasible procedure.

No such expensive and highly technical apparatus is needed for the detection of trauma to the kidneys; a routine urinalysis will suffice. In spite of this ease of assay, there is no previous study reported in the literature to date on the changes that occur in the urine of boxers following a bout.

The material for this study was obtained with the co-operation of the New York State Athletic Commission and professional boxers who fought at the Madison Square Garden and at St. Nicholas Arena in New York City during the years 1952 and 1953.

In studying the changes that occur in a man's urine after he has engaged in a boxing match, it is necessary to consider not only the factor of trauma, but also that of strenuous exercise, for it is with both factors with which we are dealing, and the effects of the latter should not be confused with those due to the constant raining of blows to the kidney region during a fight. A preliminary brief consideration of the effects of strenuous exercise on the urine is therefore in order. That urinary changes do occur following muscular exercise is a fact well chronicled in the world's physiological literature.

Following exercise there is a decrease in the urine volume. The renal plasma flow and filtration rate have been shown to be reduced markedly during exercise, the more intensive the exercise the greater the effect, thus making this blood available for circulation in active regions of the body.[3, 4, 5, 6, 7, 8]

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If the exercise is severe, it may be accompanied by albuminuria. That protein appears in the urine after strenuous exercise is interpreted as indicating that exercise induces a generalized vasoconstriction and at maximal exercise levels a large number of glomeruli drop out of function and suffer ischemia to the extent that they begin to leak protein. Erythrocytes and casts have not been reported to be found in the urine due to the effects of exercise alone.

Following exercise there is a decrease in the chloride concentration in the urine and an increase in the urinary acidity, ammonia and phosphate.[9, 10] The fall in chloride concentration may be due to the loss of chloride in the sweat and the shift of chloride from the blood into the active muscles. The rise in acidity of the urine is explained by the increased acid excretion. It has been shown that a large quantity of lactic acid may be found in the urine after short periods of severe exercise. With this excretion of acid there is an increase in the ammonia output in an effort to save base. The kidney in addition to the production of ammonia has another mechanism for the conservation of base. There is a slight increase in the phosphate excretion and the ratio of the disodium to the mono-sodium phosphate varies with the change in the hydrogen ion concentration of the urine. Since this change is in favor of the mono-sodium phosphate, base is thereby saved.

METHOD

This study was made on a group of 139 professional boxers. Of these, the comparison of urinary findings before and after a bout was made in 103; in the other 36 cases, specimens were obtained only before the fight and not afterward because either the scheduled bout did not take place, or as was the case in five instances, the boxer could not urinate immediately after the match.

A freshly voided specimen of urine was collected from each boxer on the day of the fight while he was undergoing the routine pre-fight examination in the Medical Office of the New York State Athletic Commission.

The "before" specimens were analyzed within an hour after their collection.

It is a routine procedure for a boxer to urinate before leaving his dressing room immediately before a fight.

While the bout was in progress an attempted estimate was made of the amount and severity of blows received in the region of the kidneys and a tabulation was made of the number of rounds the fight lasted.

Back in the dressing room approximately 5 to 20 minutes after the fight, another voided specimen was collected from each boxer, and these specimens were likewise analyzed within an hour of the time of their collection. The specimens were analyzed in exactly the same manner so as to obtain results which were comparable.

Each urine specimen was examined for color, turbidity, specific gravity, pH, glucose, albumin, and acetone. A well mixed sample of each was centrifuged and

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[9] Wilson, D. W., Long, W. L., Thompson, H. C. and Thurlow, S.: Changes in the composition of the urine after muscular exercise. J. Biol. Chem., 65: 777, 1925.

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a detailed microscopic examination of the sediment was performed, the final results being recorded under the high power objective

SUMMARY OF RESULTS

It was found that 46 per cent of the fighters' urines changed from clear before the bout to turbid immediately afterwards The urinary specific gravity increased in 80 per cent of the cases Traces of acetone were manifest in 14 per cent The urinary pH decreased in 39 per cent Sugar was spilled in the urine in 9 per cent of the boxers Albuminuria, which was not present before the bout, was present in 68 per cent of the boxers after the fight

Microscopically, red blood cells were found in significant pathological amount in 73 per cent of the boxers after fighting, and 26 per cent were found to have casts of granular or hyaline variety in their urine In each case, when casts were present, red cells were also present microscopically.

Small numbers of crystals, mostly calcium oxalate, were seen in 20 per cent of the boxers' urines

The data obtained from the urinalysis were broken down further in an attempt at correlating the severity of urinary changes noted after the bout with such factors as the number of rounds fought, the estimated severity of blows to the kidney region, the weight and over all protective muscle mass of the boxer, but the only factor that seemed to correlate was the number of rounds the fight lasted

For example, 65 per cent of those who fought 1–6 rounds had hematuria, while 89 per cent of those fighting 7–12 rounds had hematuria, the number of red cells present being much greater in the latter group, of whom four had total gross hematuria

Similarly albuminuria was present in 60 per cent of those who fought 1–6 rounds, and in 87 per cent of those who fought 7–12 rounds

CONCLUSION

Actually, we have proved the obvious, namely, that in addition to an effect of exercise, there is also an effect of acute trauma observed in the urine of boxers immediately after a fight, and that the degree of severity of changes noted correlates with the duration of the fight which in turn has a bearing on the amount of renal trauma

These fighters experience acute trauma to the kidneys evidenced by the finding of a high percentage of albumin, red blood cells and casts in the urine Exercise alone will not produce these changes

It is not within the scope of this paper to arrive at any conclusions as to the long range effect of the acute renal trauma experienced during the course of repeated boxing matches The door is open for further investigation into this interesting problem

This investigation should include repeated urinalyses, so that the duration of these abnormal findings may be ascertained This was attempted in our study, but, without official sanction, it was impossible to get these boxers to report back for daily follow-up studies. This should be the next step.

The question of the effect of repeated trauma on the production of scarring in the kidneys and eventual diminution of renal function should be studied. Perhaps this might best be done at present on the group of men who have grown too old to fight in the ring, and who are now retired from boxing.

It is our impression from this study that a routine urinalysis should be part of each pre-fight examination, rather than its being done just the first time a fighter is examined for license. Until further information is obtained, we recommend that a boxer not be allowed to fight until his urinary findings have returned to normal.

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WAR INJURIES OF THE UPPER URINARY TRACT

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This paper is intended as a symposium on injuries of the upper urinary tract, caused by the implements of war, as seen in the United States Naval Hospital in the U S S Repose (AH-16) during its stay in Inchon, Korea, from June 1952, to January 1953

The only cases to be considered are those which have been treated per primam in this hospital It will not include cases sent to us from Marine Medical Companies for postoperative care

In order to give the reader a clear idea of the type of casualties received, some background data are indicated Our hospital ship, during its stay in Inchon, supported the 1st Marine Division and Korean Marines We were within twenty minutes' helicopter distance from the MLR (main line of resistance) All casualties seen by us were given first aid by Battalion Aid Stations and Marine Medical Companies prior to their arrival here

The diagnosis of injury to the genito urinary tract is not difficult The salient points to be remembered are wound of entrance (and exit, if present), course of missile, presence of hematuria, and symptoms and signs of acute abdomen caused either by the injury to the genito-urinary tract or by injury to other abdominal organs The diagnosis of injuries of the penis, scrotum, testicles and urethra is obvious The methods of diagnosis will be discussed further with each particular group of injuries The urologist should not hesitate to use cystoscopy, excretory urography, etc , whenever they are deemed necessary There are few actual contra-indications to cystoscopy and retrograde pyelography If a patient is not in shock, and diagnosis is in question, cystoscopy may save the surgeon considerable work at the time of operation or may save the patient a second procedure at a later date The latter is particularly true when injury to the ureter is suspected, e g we have performed cystoscopy on a patient in bed, in the presence of a hip spica cast to determine whether a ureter had been injured, since a large metallic foreign body was lying on the psoas muscle along the course of the ureter, and the total urine output had decreased since injury

It is important to remember that injuries of the upper genito urinary tract (ureters and kidney) are more than likely to be associated with injuries of other abdominal viscera This necessitates a complete abdominal exploratory in almost every case to determine the extent of injury and will undoubtedly save more lives than any other single procedure carried out on the patient This fact will be made more clear in the remainder of this paper

INJURIES OF THE KIDNEY

A number of classifications of renal trauma have been proposed in the literature Some consist of describing the actual lesions seen in the kidney such as

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TABLE 1. *Injuries of the kidney*

CASE	WOUND ENTRANCE	*CLINICAL FINDINGS*	CONDITION OF PATIENT PREOP.	INCISION FOR EXPLORATORY	GU TRACT INJURIES	ASSOC. VISCERAL INJURIES	OP. TREATMENT FOR GU INJURY	CONDITION POSTOP.
1	Rt. flank	Hematuria, *acute* abdomen	Good	Rt. transverse abdominal	Contusion of rt. kidney	Contusion of hepatic flexure of colon	Rt. retroperitoneal space drained	Good
2	Lt. anter. abdomen	Hematuria, acute abdomen	Fair	Lt. rectus	Small shallow laceration on surface of lt. kidney	Penetrating wounds of ileum & descending colon	Lt. retroperitoneal space drained	Complications from other injuries with subsequent recovery
3	Multiple wound of lt. ant. abdomen	Hematuria, acute abdomen, lt. flank and lt. CVA tenderness	Shock	Lt. pararectus	Small laceration of upper pole of lt. kidney	Perforating wounds of ileum & jejunum	Lt. retroperitoneal space drained	Good
4	Lat. aspect of rt. lower chest	Hematuria, sucking wound of rt. chest, acute abdomen	Shock	Rt. thoraco-abdominal	Perforating wound of upper pole of rt. kidney	Perforating wound of lower lobe, rt. lung	Suture of kidney wound	Good
5	Rt. infero-lat. chest wall	Hematuria, acute abdomen	Shock	Rt. thoraco-abdominal	Perforating wound of upper lobe, rt. kidney	Perforating wound of lower lobe, rt. lung; laceration of rt. lobe of liver	Suture of kidney wound	Good
6	Rt. flank	Hematuria, *acute* abdomen, coma	Shock	Rt. rectus	Rt. kidney split	Laceration of hepatic flexure of colon (see case presentation)	Rt. nephrectomy	Died (cause of death was laceration of rt. cerebral hemisphere)
7	Post. aspect of rt. flank	Hematuria, acute abdomen	Shock	Rt. rectus	Upper half of kidney split	Laceration of rt. lobe of liver; perforating wound of hepatic flexure of colon	Rt. nephrectomy	Good
8	Rt. lower chest anteriorly	Hematuria, acute abdomen	Shock	Rt. thoraco-abdominal	Stellate laceration of central portion of rt. kidney	Perforating wound of lower lobe, rt. lung; laceration of rt. lobe of liver	Rt. nephrectomy	Good
9	Lt. flank	Hematuria	Good	Upper lt. transverse abdominal	Laceration of central portion, lt. kidney	Laceration of spleen	Lt. nephrectomy	Good

laceration, contusion, etc , and others group various types of lesions into three categories I minor, II major, III critical Minor includes those injuries causing parenchymal damage without rupture of capsule or extension into pelvis, major includes parenchymal damage and capsular rupture with almost invariable extension into pelvis and calyces, and critical includes extension of lesion to vessels of renal pedicle

For the sake of practicality, the types of renal injuries to be presented will be grouped according to the treatment which was required and carried out (table 1)

Type I Injuries requiring no direct treatment These include contusions of the kidney, caused by a blow on the outside, or by the force of a missile passing close to the kidney, or by a missile lightly striking the kidney, and small laceration of renal capsule and outer cortex where on exploration the bleeding has stopped and the kidney appears undamaged otherwise

Clinically, there is usually microscopic hematuria and occasionally gross hematuria, pain in the involved flank or costovertebral angle with splinting of the adjacent muscles, and evidence of a blow or a wound in or near the involved region If there is associated injury to abdominal viscera, there will be symptoms and signs of an acute abdomen Shock will be present only if other organs, etc , have been damaged severely In some cases, there is associated chest injury which may or may not require a thoracotomy If the latter is carried out, it will be easy to determine whether or not the missile could possibly have struck the kidney, an uninjured diaphragm and the absence of signs of abdominal injury will usually obviate the necessity of further abdominal and retroperitoneal exploration In rare cases, the kidney can be ruptured by a proximal blow This will, of course, produce symptoms which will make one suspect such a condition

If there is no associated injury to abdominal viscera, making an exploratory laparotomy unnecessary, retrograde pyelograms should be done to determine the extent of renal injury This will reveal intact pelvis and calyces

In every case of abdominal injury the renal areas should be palpated and observed as part of the laparotomy If the missile has perforated the posterior peritoneal wall, the retroperitoneal space should be explored In this way the kidney and adjoining structures can be visualized to determine whether or not they have been injured In cases where it is necessary to explore the retroperitoneal space, it is oftimes necessary to drain the area

One finds that in these types of cases the hematuria will usually disappear or become less within 72 hours The kidney should function normally and no complications should develop from the renal injury

Case 1 A 21 year old U S Marine was hit by enemy mortar fire sustaining wounds of right flank, arms and both lower extremities Examination revealed blood pressure 120/60, rigid abdomen with tenderness throughout but more marked on right, and multiple wounds of extremities Catheterized urine specimen was grossly bloody X-ray of abdomen revealed two intra-abdominal metallic foreign bodies in the right upper quadrant

An exploratory laparotomy was carried out through a right transverse incision A contusion of the hepatic flexure of colon was noted along with a contusion of the retroperitoneal wall overlying the right kidney. The retroperitoneal space was free of blood and the renal cortex was intact. The right retroperitoneal space was drained and the wound closed in the usual manner. Other wounds were adequately debrided.

Postoperatively, the urine contained blood for 36 hours, then completely cleared. Right flank tenderness persisted for 7 days. Patient did well otherwise.

Case 2: A 28 year old U. S. Marine was hit by enemy mortar fire sustaining wounds of left side of abdomen and neck. On examination blood pressure was 116/82, abdomen was rigid and acutely tender throughout, and there was slight tenderness in the left costovertebral angle. The urine was grossly bloody.

Exploratory laparotomy was carried out through a left rectus incision. There were penetrating wounds of the descending colon and ileum. Upon exploration of the left retroperitoneal space, a small shallow laceration was observed on the anterior surface of the kidney. The latter was no longer bleeding and the remainder of the kidney was intact. The retroperitoneal space was drained through a stab wound; perforations of the ileum were sutured, and a colostomy was carried out through stab wounds. The missile was removed from the neck and wounds were debrided and drained.

Urine was free of blood one day postoperatively. The patient had other complications as a result of other injuries, but this is beyond the scope of this paper.

Case 3: A 22 year old U. S. Marine hit by enemy mortar fire sustained multiple wounds of the abdomen. Patient was in mild shock when brought into one of the forward medical companies. He was given blood and sent here by helicopter. On admission, his blood pressure was 105/72. Examination revealed wounds of extrance on the left lateral aspect of the abdomen at the level of the umbilicus. There was marked rigidity and tenderness of entire abdomen. The left flank and the left costovertebral angle were also markedly tender. The urine was grossly bloody.

An exploratory laparotomy was carried out through a left pararectus incision. There were multiple perforations of the ileum and the jejunum which were sutured primarily. A small hematoma was present in the left retroperitoneal space with perforation of the retroperitoneal wall near the upper pole of the left kidney. There was a small laceration of the upper pole of the kidney. The bleeding had stopped and the remainder of kidney was unharmed. No direct treatment was given to the kidney. The retroperitoneal space was drained through a stab wound in the left flank. The left colic gutter was drained and the abdomen closed in the usual fashion.

The postoperative course was uneventful with the exception of ileus which was easily handled with intubation. The urine remained loaded with red blood cells and white blood cells for 4 days after which it cleared considerably. By the time the patient was evacuated, the urine contained only a few white blood cells and red blood cells. His condition was good.

Type II. Injuries of kidney neccessitating repair. These include injuries of renal substance in which repair is possible by means of simple suturing, partial nephrectomy, or other procedures. Injuries of this sort can be minimal or severe.

They can include a laceration of renal cortex in which suture of renal substance is required for hemostasis, a laceration or perforation of renal substance with extension into calyx in which accurate suture of laceration including calyceal tear is necessary not only for hemostasis but to prevent subsequent fistula formation, and severe damage to upper or lower pole of kidney in which a partial nephrectomy is necessary to save the remainder of the kidney.

The diagnosis will be suspected upon noting the wound of entrance and course of missile. The clinical picture of such an injury varies with the extent of damage. The patient will almost invariably have hematuria, he may or may not be in shock, he will have flank and costovertebral angle tenderness, a retroperitoneal mass may be palpated or visualized on plain x-ray, signs of an acute abdomen may be present, and urography will show extravasation of dye, if the injury has included the calyceal system. In the majority of instances an associated injury to other abdominal viscera will be present, and symptoms and signs of an acute abdomen will prevail. Associated injury to thoracic structures is not uncommon, the clinical picture characteristic of such an injury will of course present itself.

Case 4. A 24 year old Korean Marine was hit by enemy grenade fragments, sustaining wounds of the right lower chest and the right side of the abdomen. The urine was grossly bloody. Examination revealed a sucking wound of the right lower chest (lateral) with diminished breath sounds in the right chest, the mediastinum was shifted slightly to the left. There was a small wound in the right lower quadrant of the abdomen. The abdomen was rigid and acutely tender. Patient was in shock when brought in by helicopter. He required 1000 cc whole blood prior to surgery.

X rays revealed missiles in the right retroperitoneal area near the upper pole of the right kidney.

The patient was explored through a right thoraco-abdominal incision. A wound of the lower lobe of right lung was found sealed. There was a perforating wound of the upper pole of the right kidney which was bleeding freely. Hemostasis was established by means of interrupted mattress sutures tied over pieces of fat. A laceration of the right lobe of the liver was sutured with interrupted mattress sutures of ribbon catgut. The retroperitoneal area was drained through a stab wound, the liver area was drained through the incision. A thoracostomy tube was left in the chest.

The postoperative course was entirely satisfactory. The retroperitoneal drain was removed 5 days postoperatively, and the thoracostomy tube was removed in 48 hours. The abdominal drain was removed in 8 days because of bile drainage. The chest was clear by x-ray 8 days postoperatively. Tenderness in right upper quadrant persisted up to the time of evacuation. There was no bile drainage, and the urine was clear.

Case 5. A 27 year old Korean Marine hit by grenade fragments sustained wounds of right arm, right lower extremity and right flank. Patient was sent to this hospital by helicopter.

Examination revealed patient to be in shock, blood pressure 60/20, pulse 90 and very thready; wounds of right upper arm, right knee, and right inferolateral chest. The abdomen was rigid and tender. The urine was grossly bloody.

The patient was given blood on admission to combat shock. When his condition permitted, patient was taken to the operating room and explored through a right thoraco-abdominal incision. The right chest was emptied of blood; a small wound of the lower lobe of right lung needed no suturing as it had sealed. A small perforation was present in the right leaf of diaphragm. The right lobe of the liver had a laceration about 7 cm. long extending from the superior to inferior surface. This was sutured interruptedly with ribbon catgut. There was a retroperitoneal hemorrhage in the region of the right kidney. Exploration of this area revealed a through and through perforation of the upper pole of the right kidney. This was repaired by mattress sutures taken over a piece of muscle. Penicillin, 300,000 units and 0.5 gm. streptomycin were placed in the chest. Drains were placed retroperitoneally and under liver. A tube was left in the chest. Closure was carried out in the usual manner. The other wounds were debrided.

Postoperatively, the patient did well. He voided clear urine on the third postoperative day. The thorocostomy tube was removed on the third day. All drains were removed ten days postoperative. Cystoscopy was performed 25 days postoperative and retrograde studies were carried out. The right kidney appeared normal with good function. The patient was evacuated for further convalescence.

Type III. Injuries of kidney necessitating nephrectomy. A policy of conservatism was carried out with regard to nephrectomy for the treatment of kidney injuries. The conservation of renal tissue was of prime consideration in every case of severe kidney injury. In cases where kidney injury was observed, the presence of the contralateral kidney was always checked; in this manner it was possible to estimate whether or not that kidney was normal in size and consistency. In this series, nephrectomy was carried out in those cases in which the kidney was damaged beyond repair, and where it was necessary to tie off the renal pedicle to stop the hemorrhage. There was no difficulty in determining whether a kidney was beyond repair. In these cases the kidney was severely lacerated, enclosed in a massive hematoma, and was bleeding profusely.

It will be seen that the cases to be presented below are all surgical emergencies. Shock was present in almost every case, as was gross hematuria and the findings of an acute abdomen. In four of the five cases there was associated injury to other abdominal viscera; in one there was associated injury to intrathoracic viscera. A retroperitoneal mass was present in every case but could not be palpated because of the extremely rigid abdomen. These patients invariably received blood at a medical company before reaching this hospital.

Diagnostic studies were unnecessary in these cases as they were treated as emergencies. Exploratory procedures were carried out as soon as patient's condition would permit.

Case 6: A 22 year old Marine hit by enemy grenade fragments sustained wounds of the right flank and bridge of nose. Upon arrival, his blood pressure was 80/60. His abdomen was rigid, urine was grossly bloody, and he was bleeding profusely from a wound of his face. The patient was in coma, and his condition was critical. After receiving two pints of blood, his pressure rose to 92/68. An abdominal exploratory was carried out through a right rectus incision. The peritoneal cavity was full of blood. The hepatic flexure of colon was raggedly lacerated. A massive retroperitoneal hematoma was present on the right. The retroperitoneal wall was incised and renal area exposed. The right kidney was enclosed in the hematoma. The kidney was found split in its central portion. In attempting to further visualize kidney, a profuse hemorrhage was started. After clamping the pedicle, the hemorrhage was controlled. The pedicle was cut and tied, and the kidney removed; however, the blood pressure had dropped once more and patient expired on the operating table.

Postmortem examination revealed, in addition to the aforementioned findings, a lacerated right cerebral hemisphere caused by the missile which entered through the nose and lodged in the occipital bone after traversing the brain.

Case 7: A 19 year old private, USA, hit by enemy shrapnel sustained wound of the right side of the abdomen in the region of the mid flank. The wound of exit was posterior to wound of entrance. Examination of abdomen revealed it to be rigid and tender throughout. A catheterized urine specimen was grossly bloody. Stomach aspirations were negative. X-ray revealed a large metallic foreign body lodged in the anterior abdominal wall, and the wound of entrance to be posterior. The patient received 3 units of whole blood. The blood pressure was 120/70 at the time of surgery; he had been in shock when he was received by the forward medical company. The patient was brought to the ship by helicopter in satisfactory condition.

The patient was explored through a right rectus incision. Blood and fecal material welled up from within the peritoneal cavity. A large rent was seen in the retroperitoneal wall on the right. There was a profuse hemorrhage coming from the retroperitoneal space. The kidney was isolated and pedicle clamped and tied. The kidney was then removed. Its upper half was found split. A small laceration in the right lobe of the liver was repaired with ribbon catgut sutures. A perforation of the hepatic flexure of colon was repaired and an ascending colostomy was carried out, between Kocher clamps, in the center of the abdominal incision. The metallic foreign body was removed. Wide debridement and drainage of the retroperitoneal space and peritoneal cavity was carried out.

The patient tolerated surgery well. His postoperative condition was satisfactory. Prognosis is excellent.

Case 8: A 22 year old corporal, USMC, shot by sniper sustained bullet wounds of right chest and abdomen. The bullet entered at the level of the ninth rib anteriorly; exit was at the level of the twelfth rib posteriorly. The patient had no dyspnea or cough. The right side of the abdomen was extremely tender. There was muscle guarding and abdominal rigidity throughout. Voided urine was grossly bloody.

The patient was taken to a forward medical company in shock. He was given 2 pints of blood and antibiotics. X-ray studies revealed the right diaphragm to be slightly higher than normal. He was sent here by helicopter. Upon admission, the blood pressure was 130/70.

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Postoperatively, the patient did well. He voided clear urine on the third postoperative day. The thorocostomy tube was removed on the third day. All drains were removed ten days postoperative. Cystoscopy was performed 25 days postoperative and retrograde studies were carried out. The right kidney appeared normal with good function. The patient was evacuated for further convalescence.

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Case 7 A 19 year old private, USA, hit by enemy shrapnel sustained wound of the right side of the abdomen in the region of the mid flank The wound of exit was posterior to wound of entrance Examination of abdomen revealed it to be rigid and tender throughout A catheterized urine specimen was grossly bloody Stomach aspirations were negative X-ray revealed a large metallic foreign body lodged in the anterior abdominal wall, and the wound of entrance to be posterior The patient received 3 units of whole blood The blood pressure was 120/70 at the time of surgery, he had been in shock when he was received by the forward medical company The patient was brought to the ship by helicopter in satisfactory condition

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The patient was taken to a forward medical company in shock He was given 2 pints of blood and antibiotics X-ray studies revealed the right diaphragm to be slightly higher than normal He was sent here by helicopter Upon admission, the blood pressure was 130/70

Through a right thoraco-abdominal incision the right chest, abdomen and retroperitoneal space were explored. There was a small hole in the lower lobe of the right lung which had sealed. A small hole was present in the right leaf of the diaphragm. This was sealed. A large laceration splitting the right lobe of liver was sutured interruptedly with ribbon catgut. There was a massive retroperitoneal hematoma surrounding and including the right kidney. There was a large stellate laceration of the central portion of right kidney. The renal pedicle was isolated, clamped, cut and tied. The right kidney was removed. The retroperitoneal space and bed of the liver were drained. The thoraco-abdominal incision was closed in the usual manner.

The postoperative course was uneventful except for beginning wound dehiscence in the upper portion of abdominal incision. This was closed with steel retention sutures under local anesthesia. Recovery is now progressing favorably at a hospital in the U.S.A.

Case 9: A 20 year old Korean Marine hit by mortar fragments sustained multiple wounds of the right side of the abdomen, extremities and left flank. His entire abdomen was tender and rigid. The urine was grossly bloody.

The patient was explored through a right rectus incision. No pathological process was noted in the right side of abdomen. Blood was seen coming from the left upper quadrant. A left transverse incision was carried out in addition. A lacerated spleen was found and removed The left retroperitoneal area was explored as a hematoma was present in that space. The kidney was found to be lacerated with bone fragments imbedded in its central portion. The renal capsule was stripped by the hemorrhage. As it was felt that a functional kidney could not be salvaged, a left nephrectomy was carried out after first isolating the pedicle so it could be clamped, cut and tied.

The retroperitoneal space was drained through a stab wound.

Recovery was uneventful.

Case 10: A 21 year old Korean Marine hit by enemy mortar fire sustained wounds of the right upper quadrant of the abdomen and right lower chest. The missile entered at level of the eleventh rib and lodged at the level of interspace T-10–11. The patient was taken to a forward medical company in shock. He was given two units of whole blood and sent to this hospital ship by helicopter. Upon examination, his abdomen was rigid with marked right side tenderness. The urine was grossly bloody; his chest was clear. X-ray revealed cloudiness of the right side of the abdomen and the location of missile at interspace of T-10–11.

The patient was explored through a right thoraco-abdominal incision. Intraperitoneal organs were unharmed. A massive hematoma filling the entire right retroperitoneal space was present. The latter was explored and the right kidney was found to be severely lacerated (fig. 1). The pedicle was isolated, clamped, and divided. The kidney was removed with surrounding fascia and adherent hematoma. Most of the clotted blood was evacuated by the handfuls from the retroperitoneal space. The latter was drained through a stab wound. The incision was closed in the usual fashion after the posterior peritoneal wall was sutured.

The patient did well postoperatively. His prognosis is excellent.

FIG. 1. Gross specimen—severely lacerated kidney

Comment: The most important information that can be gained from the preceding discussion is that injury to the kidney by a missile will almost always be accompanied by injury to other organs or viscera. It is the unusual case that will have no associated injury. Numerous postoperative cases sent to us from the forward medical companies in which the kidney had been damaged had in addition associated injury to intraperitoneal viscera, thoracic viscera or both. In view of this, a complete abdominal exploratory is indicated in every case. The severity of thoracic injury can usually be determined by clinical findings, chest x-ray and missile course, and appropriate treatment instituted as necessary.

In upper quadrant injuries of the abdomen where the possibility of liver, spleen or lung injury exists, a thoraco-abdominal incision was preferred. The incision which afforded the best exposure of kidney and adjacent viscera extended from region of umbilicus diagonally upward across the costal cartilages at the level of 7–8 ribs and into the space between those ribs. The diaphragm was split along the line of incision. Repair of the liver, splenectomy, suture of lung, nephrectomy, and complete abdominal exploratory were easily accomplished through such an incision.

In other types of abdominal injuries, a rectus or para median incision was used for the most part. Occasionally, a transverse abdominal incision was carried out, but it was not preferred. Renal exploration was carried out transperitoneally. This has a few advantages over the translumbar approach. The pedicle can be isolated very easily. The injured kidney and hematoma need not be disturbed before the pedicle is clamped, and an abdominal exploratory is more easily accomplished.

INJURIES OF THE URETER

The diagnosis of ureteral injury is usually made after the initial surgery has been done. The ureter is not readily seen during exploratory abdominal procedures unless it is specifically looked for. Ureteral injury then can only be discovered at the time of initial surgery if it is suspected primarily, which necessitates a more through exploration.

In a badly wounded patient, the course and location of the missile on a plain x-ray will be the only clues of a ureteral injury. There may be or may not be blood in the urine. If it is suspected that the course of the ureter has been traversed by the missile, a retroperitoneal exploration should be carried out in that area.

The best and surest method of diagnosis is retrograde urography. This procedure should be done prior to the initial surgery, provided the patient's condition allows such a procedure, and would thereby save the patient a second operation for the repair of his ureteral injury.

The treatment of ureteral injury varies with the extent and location of the trauma. The preferred treatment of a partial tear of the ureter is ureteral intubation with a 10F or 12F ureterostomy tube. In some of these tears, the tube should be brought out with a nephrostomy. In small tears the tube can be coiled in the bladder and removed at cystoscopy. The use of a T tube was attempted for a partial ureteral tear. This will be commented upon below.

In complete severance of the ureter, an anastomosis must be carried out if the kidney is to be preserved in its normal state. Whether or not this can be done depends on how much of the ureter has been injured. If a large section of ureter has been injured so that its ends cannot be approximated without undue tension, an anastomosis will probably be unsuccessful. The treatment of choice in such a case would be nephrectomy, provided the other kidney is normal.

Severed ends of the ureter can be anastomosed in a number of ways. We prefer an oblique type of anastomosis, placing fine atraumatic sutures through the serosa and muscularis. The anastomosis should be done over a splinting catheter, which is left in place for at least 21 days. A nephrostomy should be done at the time of anastomosis, both tubes being brought out through the same kidney incision.

Injuries of the lower portion of the ureter can sometimes be treated by a ureteroneocystostomy. It is preferable to anastomose the ureter as close to the posterior wall of the bladder as possible. An anastomosis into the dome of the bladder should be done only if the length of the ureter is such that it can be brought down no farther. A splinting catheter should be used in these cases also. This can be brought out through the urethra. A Foley catheter inserted through the urethra alongside the splinting catheter is a great help in stabilizing the latter.

Four cases of ureteral injuries were seen; one of these was treated at another hospital. Another patient was seen in consultation at a Korean hospital seven months after the original injury. It will be mentioned in passing and not included in the case presentations

Our first introduction to ureteral injury was a Korean soldier who had been wounded 7 months prior to the time he was seen. A urinary fistula had developed in the left flank. Excretory urogram revealed the fistulous tract to arise from the ureter about 6 cm. below the ureteropelvic junction The patient had sustained wounds of the small intestine and ureter. The former had been repaired but the latter remained untreated. Subsequently a retroperitoneal abscess developed and was drained; otherwise, the patient received no treatment for the ureteral injury. When asked to see the patient in a Korean hospital, he was beyond the stage in which a ureteral repair could be accomplished. A left nephrectomy was done thereby curing his fistula.

Case 11: A 32 year old Korean was hit by shrapnel sustained wounds of the abdomen and extremities. He was initially explored at a Marine Medical Company where 15 inches of small intestine were removed, and an end-to-end anastomosis was carried out His other wounds were debrided and dressed. Twenty-four hours postoperative, his abdomen became distended. A Levine tube was inserted which relieved the distention considerably. The patient was sent to this hospital 13 days postoperative. His abdomen was distended with fluid. A paracentesis yielded 6050 cc of straw colored fluid He complained bitterly of left flank pain. His left flank was distended and dull to percussion. A tap of that area yielded straw colored fluid with a specific gravity of 1.013. Cystoscopy was then performed and a retrograde pyelogram made (fig. 2). On examining the bladder, no urine was seen coming from the left ureteral orifice. Clear urine was spurting from the right. A 5F ureteral catheter was passed 26 cm on the right with ease. On the left, obstruction was met at 15 cm. Urography revealed a perforation of the ureter at that point with extravasation of dye into the adjacent area Some dye reached the left kidney which revealed moderate dilatation of the pelvis and calyces.

The patient was taken to surgery and operated on through a left lumbar incision The ureter was exposed and the tear isolated. As the ureter was not completely severed, a T tube was inserted and the retroperitoneal space drained. The missile which caused the damage was removed from the body of the vertebra adjacent to the damaged portion of the ureter.

The postoperative course was uneventful and the patient did well and was up and about in 3 days Ten days later, the T tube was removed However, the ureterocutaneous fistula thus formed did not heal. The patient was again explored 2 weeks later through a left lumbar incision and the fistula was isolated There was much scar tissue present at the former site of injury. Freeing the ureter and removal of the scar tissue required complete severance of the ureter. An oblique anastomosis around a splinting tube was carried out This tube was brought out with a nephrostomy tube The patient did well postoperatively. He was evacuated to a Korean hospital 20 days later The followup is not available.

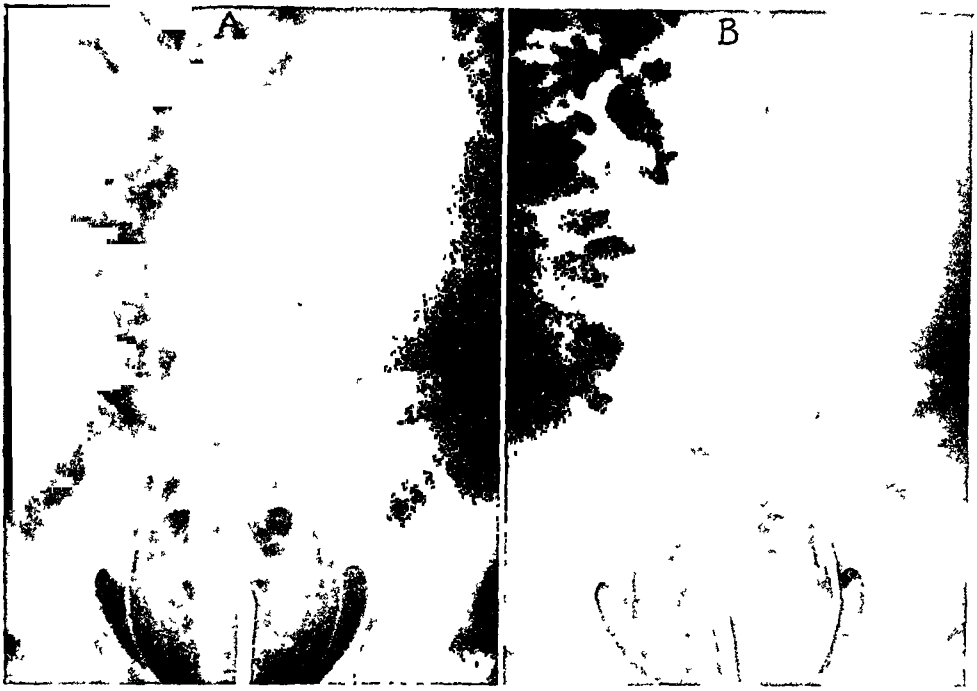

FIG. 2. *A*, left ureteral catheter passed to point of injury. Shrapnel seen at site of injury. *B*, retrograde ureteropyelogram reveals laceration of ureter with pooling of dye lateral to it.

It is quite possible that proper healing of the ureter would have taken place had the T tube been left in place for at least 21 days.

Case 12: A 19 year old private first class, USMC, hit by fragments from an exploding land mine, sustained multiple wounds of the lower extremities, along with a compound comminuted fracture of the left tibia. The patient had no findings suggestive of abdominal or chest injury at this time. He was taken to the operating room where debridement of his wounds was carried out. A Steiman-pin was inserted into the left tibia in preparation for an intramedullary nailing which was carried out 12 days later.

Twenty-seven days after the initial injury, the patient experienced a severe right lower quadrant abdominal pain which radiated into the right testicle and right costovertebral angle. The patient was in agony. Examination revealed muscle guarding of the right side of the abdomen with marked tenderness in the right costovertebral angle and flank. Urinalysis was normal. It was suspected that patient was having right ureteral colic. An excretory urogram revealed a nonfunctioning right kidney and a normal left kidney. A metallic foreign body was lying just lateral to the course of the lower ⅓ of the right ureter. Cystoscopy was performed. The right ureteral orifice was edematous and the intramural portion of the right ureter was dilated. The tip of the ureteral catheter could not be inserted into the orifice of the right ureter. No opaque shadows were seen along the course of the right ureter.

As the right lower quadrant of the abdomen became increasingly tender and the patient had no relief from his pain, it was decided to do an exploratory laporotomy. He was explored through a right rectus incision. The peritoneal cavity was negative so the peritoneum was closed. An extraperitoneal exploration was then carried out by reflecting the peritoneum medially The right ureter was dilated and tense in its lower portion Dissection down to ureterovesical junction was carried out There was no stone palpable in the lower ureter The ureter was then opened and a ureteral catheter inserted An attempt to pass a catheter into the bladder was unsuccessful as an obstruction was present in the intramural portion of the ureter The bladder was then opened to facilitate further exploration The intramural portion of the ureter was found to be scarred and strictured This was most likely caused by the aforementioned missile traversing this portion of the ureter A ureteroneocystostomy was carried out by means of the "fish-mouth" technique and the bladder was closed primarily Drains were left extraperitoneally along the paravesical space

The patient did well after operation His pain was relieved and healing was progressing favorably when he was transferred to a Naval hospital in Japan

Comment: The few cases of ureteral injuries seen serve to emphasize the fact that these cases are difficult to recognize initially If the path of the missile had been traced in case 10, the diagnosis could have been made and the injury treated initially This is to the patient's advantage, as the second procedure is always rendered difficult by adhesions, infection, urine in the tissue spaces, and the weakened condition of the patient A preoperative excretory urogram in cases suspected of ureteral injury is sometimes all that is necessary, although the recommended procedure is cystoscopy and retrograde urography It is well to re-emphasize that the injury of the ureter has to be *suspected* if it is to be diagnosed initially The condition of the patient and the facilities available will determine what should be done to confirm one's suspicions of ureteral injury

SUMMARY

A symposium of war injuries of the upper urinary tract and illustrative cases have been presented The incidence of abdominal and chest injuries have been reduced, as compared with World War II, as a result of the use of the so called "armor-vest" The incidence of postoperative infection with resultant complications, as compared with World War II, has been reduced by the liberal use of antibiotics after injury and operation These advances, along with the excellent treatment given the wounded in the forward aid stations, have salvaged many lives from the field of battle

ACKNOWLEDGMENTS

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THE PROBLEM OF PRIMARY MEGALO-URETER

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In recent years congenital anomalies of the urinary tract in children are being recognized and reported in the literature in increasing numbers. This has resulted to a great extent from the wider recognition of the principle that a persistent urinary tract infection calls for detailed examination.

Among these abnormalities dilatation of the ureter, unilateral or bilateral, is no longer a rarity. Campbell[1] has classified such dilatations into two groups, primary and secondary. A diagnosis of primary megalo-ureter should be confined to those cases in which no mechanical obstruction can be found to account for the ureteral dilatation. The term megalo-ureter was first used by Caulk[2] in 1923 to describe such a deformity in a case in which no obstructive lesion was demonstrated and in which the ureteral orifices appeared normal on cystoscopic examination. Prior to this, similar ureteral dilatation without apparent cause had been noted by other observers (Saintu[3] 1896, Fortescue-Brickdale[4] 1905, and others).

The purpose of this paper is to review the results of some methods of treatment used for this condition in the past, and to consider briefly whether the operative procedures have yielded significant clinical benefits. It would be tempting also to discuss the etiology of megalo-ureter, but with the evidence available in the cases presented here, any conclusion reached would be largely speculative.

Before making a diagnosis of primary megalo-ureter it is well to remember its rarity. Such a diagnosis was made in only 4 patients admitted to University Hospital since 1935: two further cases have been excluded from the present study owing to inadequate record of bladder function. Similarly, Campbell[5] could only find two cases of primary megalo-ureter among several hundred cases of dilatation of the ureter. To establish the diagnosis two criteria must be fulfilled:

1. DILATATION OF THE URETER

Ureteral dilatation may be demonstrated by excretory or retrograde pyelography, or by cystogram if reflux of urine from bladder to affected ureter is present. The value of a delayed or voiding cystogram is emphasized, for in some cases no sign of reflux is found in early films but is only observed in those made after an interval of one-half hour or an hour (Stewart[6]).

Presented to the New York Section of the American Urological Association, April 22, 1953.

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The diameter of the ureter is increased; this may be unilateral or bilateral. In the present study it has been noted that the circumferential dilatation is not accompanied by commensurate increase in length, and kinking of the ureter is not a marked feature of these cases. A similar observation has been made by others (Campbell,[5] Hepler[7], Wayman[8]), and Hinman[9] has considered multiple angulation to be indicative of an obstructive etiology. The renal pelvis and calyces of these patients do not show the degree of dilatation which might be expected in the presence of such ureteral deformity.

2. ABSENCE OF OBSTRUCTION

Obstruction in the course of the lower urinary tract must be excluded. The more gross types of obstructive lesion at the lower end of the ureter or at the bladder neck should present no difficulty in demonstration. But exclusion of obstruction at the bladder level cannot be regarded as certain without careful assessment of vesical function by cystometric examination and estimation of residual urine. Bladder dysfunction due to neurogenic disturbances may be reflected in the ureter, and many reported cases of so-called primary megalo-ureter would properly be excluded from this group if such full investigation had been carried out.

It is an accepted fact that long standing ureteral infection can produce some degree of dilatation of the ureter. With this knowledge it would be desirable, before establishing a diagnosis of primary megalo-ureter, to exclude infection as a possible etiological factor. In the present series of cases, however, infection is an invariable accompaniment of the stasis associated with ureteral dilatation. For this reason it is felt that cases with infection should not be excluded from this category if the criteria mentioned above are fulfilled.

Some observers on this subject have stated that additional criteria are necessary to confirm the diagnosis of primary megalo-ureter. Campbell considers that vesico-ureteral reflux with a relaxed immobile ureteral orifice is a characteristic finding in this condition. Although reflux may be present, it appears not to be invariably the case; reflux occurred in only one of the 4 patients presented here (case 1). Indeed its absence tends to confirm a diagnosis of primary ureteral dilatation provided that an obstructive lesion of the lower ureter has been excluded. Also, on cystoscopy we are impressed with the normal appearance of the ureteral opening in these cases and have observed patulous orifices in only one case.

CASE REPORTS

Case 1. An 11 year old girl, S. P., was first seen in August 1950. Her mother gave a history that the child was well until two years old when she had a convulsion accompanied by temperature of 102F. During the course of illness, which lasted a few days, her doctor found that she had a urinary tract infection which responded promptly to treatment with a sulfonamide preparation. This was the first attack of many similar episodes which occurred at intervals of three to five months and all were accompanied by the presence of pus cells and organisms in the urine. Since the age of eight it had become increasingly difficult to control the infections and attacks had become prolonged. Her mother stated that she appeared to have no difficulty in passing urine at any time.

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[7] Hepler, A. B.: Non obstructive dilatations of upper urinary tract in children. J. A. M. A. 109: 1602, 1937.

[8] Wayman, T. B.: Surgical treatment of megalo-ureter. J. Urol., 61: 883, 1949.

[9] Hinman, F.: Obstructive hydroureteral angularity with hydronephrosis in children. Arch. Surg., 18: 21, 1929.

The patient was a healthy looking girl of normal size and weight and no gross abnormality was found on physical examination. She voided urine with good force although 55 cc residual urine was present following micturition and this showed 10 to 15 white blood cells and rod shaped organisms when examined microscopically. Renal function tests were within normal limits. A cystometrograph was performed at this time and although there was large bladder capacity (400 cc) the shape of the curve was normal. Panendoscopy and cystoscopy (August 16, 1950) revealed a normal bladder with no trabeculation and no vesical neck obstruction. Both ureteral orifices were patulous and were easily catheterized; on retrograde injection of dye moderate increase in ureteral diameter was noted. A cystogram revealed the presence of bilateral ureteral reflux.

At operation on August 18, 1950, the left ureter was exposed throughout its length by a left pararectal incision. It was found to be dilated to three times its normal size but showed active peristalsis on stimulation. The dilatation continued to the point where the ureter entered the bladder. The caliber of the ureter was reduced throughout its length by removal of a strip comprising approximately two thirds of its circumference as described by Crabtree and also used by Wayman. The lower end of the ureter was then re-implanted into the bladder by a fish-mouth technique. The operation was completed by suprapubic cystotomy.

The patient made a good recovery from operation and in view of the ureteral reflux her cystotomy drainage was maintained to insure continuous and complete bladder drainage. However, repeated episodes of urinary tract infection occurred which could be controlled by various antibiotic agents. A cystogram made on October 31, 1950, showed that ureteral reflux persisted bilaterally. Three months after operation, following a trial of voiding with the suprapubic tube clamped, only a few cubic centimeters of residual urine remained in the bladder and her suprapubic drainage tube was removed. The removal of the suprapubic tube appeared to lessen the frequency of attacks of urinary infection, and a cystogram made one year later demonstrated diminution in reflux on the right side but it was still present on the left. Since this time she has continued to make very satisfactory progress with only one attack of urinary infection during the the past year and recent excretory urograms give evidence of good renal function with no hydronephrosis.

Commentary on case 1: This was the only case of the series in which ureteral reflux was demonstreated preoperatively. It is significant that she was found to carry residual urine of 50–100 cc although she was observed to void with an uninterrupted and forceful stream with apparent complete emptying of the bladder. In view of the normal vesical function it was assumed that this amount of residual urine did in fact represent the volume of reflux. Crabtree[10] has reported a similar case in which incompetence of the ureteral valves allowed reflux of urine during voiding.

In this case a period of 3 months' vesical drainage by cystotomy did not diminish reflux nor did it improve the degree of megalo-ureter on either side. It is noteworthy that following removal of the suprapubic drainage tube her pyrexia subsided and urinary infection markedly improved. A cystogram made 13 months after operation revealed only minimal reflux into the lower third of the ureter on the right but was still present on the opposite side which had been treated surgically. Although the left ureter was poorly visualized in this cystogram the x-ray suggested that the left ureter was in fact as dilated as before operation. The last excretory urogram made in August 1952 (two years after operation) shows good renal function on both sides with no evidence of hydronephrosis or calyceal dilatation. This fact coupled with the satisfactory clinical progress that the child is making is strong evidence that little benefit was derived from operation. It would be interesting to know the degree of ureteral reflux which may now be present, but the mother is reluctant to bring her child to the hospital for this purpose as she is making such excellent progress.

Case 2. J. O., a girl, was brought to University Hospital in July 1950, when 4 years old. She had been well until the age of 18 months when her mother noticed that she had pain on urination. At this time her doctor found pus cells in the urine. Since this first attack she had had four episodes of pyrexia accompanied by frequency of micturition every one to two hours and an infected urine. At no time was there a history of flank pain or tenderness on palpation in the renal areas. Physical examination was negative and tests showed satisfactory renal function (blood urea nitrogen 16 mg. per cent; phenolsulfonphthalein excretion 48 per cent in 2 hours). An excretory urogram revealed a severe degree of bilateral ureteral dilatation with minimal hydronephrosis on the left. No evidence of ureteral reflux was demonstrated in a cystogram.

At operation on July 28, 1950 the right ureter was found to be approximately 2 cm. in diameter but showed good peristalsis. The dilatation extended from the kidney to a point approximately one inch from the bladder. At this point the ureter was of normal size and through this narrowed portion a No. 6 ureteral catheter was passed with ease into the bladder. It was therefore felt that obstruction at the lower end of the ureter could be confidently excluded. The ureter was detached from the bladder at the ureterovesical junction and this narrower portion excised. Approximately one-third of the diameter of the ureter was resected throughout its length and re-implanted into the bladder by an elliptical anastomosis at a point above and to the right of the previous ureteral opening. The ureter was drained by ureterostomy and a cystotomy tube was left in situ suprapubically. A cystogram made 3 months after this operation now showed reflux on the operated side.

On October 9, 1950, at a second operation, exposure of the left ureter showed

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[10] Crabtree, E. G.: Plastic operation for the relief of megalo-ureter. Trans. Amer. Assoc. G. U Surg., 30: 311, 1937.

similar findings to those on the right side. Again no evidence of obstruction could be demonstrated at the lower end of the ureter and approximately 4 inches of the lower ureter were resected and the free end re-implanted into the bladder by elliptical anastomosis. On this side no longitudinal segmental resection was performed. A cystogram made one month following this procedure now revealed that reflux was present bilaterally.

The child made satisfactory progress following these operations and 2 months after the second operation the cystotomy tube was removed and the suprapubic fistula allowed to close. At this point severe episodes of pyrexia occurred and could only be controlled by sustained catheter drainage. From then until the present time removal of the indwelling catheter has invariably been accompanied by a recurrence of these attacks of pyrexia and flank pain. A recent excretory urogram (fig. 1, *A*) showed satisfactory function although ureteral dilatation persists and on cystogram (fig. 1, *B*) it is seen that she has a severe degree of megalo-ureter and hydronephrosis. At no time during the course of this patient's illness and treatment have renal function tests revealed any gross deviation from normal.

Commentary on case 2: In this case, although the dilatation of right ureter appeared to be initially improved by operation, the final result and persistence of megalo-ureter show that surgery did little to benefit the child. In fact, ureteral reflux which was not present in the original x-rays appeared in cystograms made after operation. It is significant that continuous bladder drainage produced no improvement in her ureteral dilatation.

In spite, however, of these abnormalities and a urinary infection from which she is seldom free, the child remains surprisingly active and healthy; this fact is reflected in the comparatively normal renal function tests.

This case also illustrates the value of a cystogram in demonstrating the true degree of ureteral dilatation. The excretory pyelogram (fig. 1, *A*) does not suggest the gross megalo-ureters which in fact exist, but which are dramatically revealed in a cystogram made shortly afterwards (fig. 1, *B*).

Case 3. A 4 year old girl, L. A., was admitted to hospital in March 1952. For

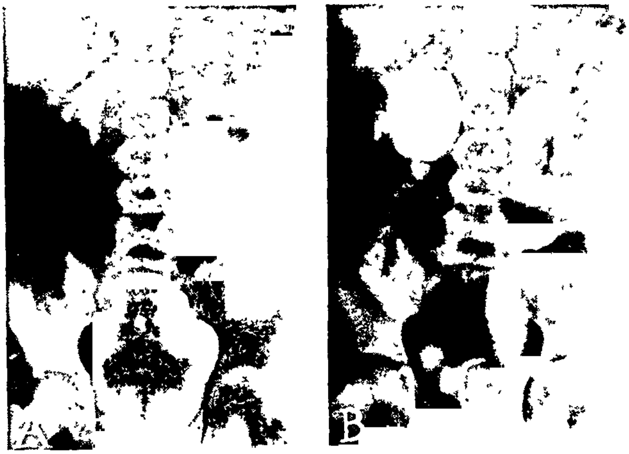

FIG. 1. Case 2. *A*, excretory urogram and *B*, cystogram 2 years after operation showing recurrence of dilatation of right ureter. Cystogram reveals true degree of ureteral dilatation which is not demonstrated in excretory urogram made 2 days previously.

two and a half years she had suffered from recent episodes of high fever, frequency and pain on micturition. During each of these attacks her urine was found to contain pus cells and bacteria, and although initially the infection responded rapidly to treatment with sulfa drugs it had recently become refractory to therapy. At no time had there been any difficulty in initiating micturition.

On admission, physical examination was negative and she was seen to void with a good stream. A catheter specimen of urine examined microscopically showed 5 pus cells per high power field, and numerous bacilli which proved on culture to be E. coli. The blood urea nitrogen was 17.5 mg. per cent, the plasma CO_2 combining power 38 vols. per cent, and serum chlorides were 103 m/Eq. per liter.

Excretory urograms revealed dilatation of both ureters, with some degree of hydronephrosis on the left. The calyces, however, were sharply outlined with no loss of "cupping." A cystogram showed no evidence of reflux. A normal cystometrograph and absence of residual urine after voiding suggested good bladder function. On cystoscopy and panendoscopy the bladder appeared normal, with an adequate vesical neck outlet. No ureterocele or other obstruction was seen at either ureteral orifice, through which No. 5 catheters could be passed with ease.

At operation on March 31, 1952, the lower third of the left ureter was exposed extraperitoneally by a transverse lower abdominal incision. The ureter was approximately 2 cm. in diameter throughout its course until, at a point 3 cm. from the bladder, the dilatation ceased and the remaining portion of the ureter appeared to be of normal size. Active peristalsis was noted in the dilated portion of the ureter. The ureter was divided at its junction with the bladder and the narrowed section removed, together with 3–4 cm. of the dilated portion. The remaining ureter was re-implanted into the bladder at a point higher on the lateral wall, by elliptical anastomosis. A pathological report of the removed portion read as follows: "Dilatation of the ureter with hypertrophy of muscularis and heavy focal collections of lymphocytes in the muscularis."

The patient made a good recovery from operation, but convalescence was complicated by attacks of high temperature and pain and tenderness in the left costovertebral angle. Vigorous therapy with antibiotic drugs during the next 3 months was required to control these episodes of infection but her flank pain became progressively more severe.

A cystogram made at this time revealed reflux of urine on the side of operation, and it was believed that these symptoms were due to an ascending pyelonephritis. During July 1952 she had persistent pyrexia, her general condition deteriorated and the child became pale and listless. Although studies showed good renal function, urgent treatment was considered necessary to prevent severe renal damage and possible nephrectomy.

Accordingly, at a second operation on August 11, 1952, the left ureter was excised in its entirety, and replaced by an isolated segment of ileum as reported by McLean and Fais[11] following its experimental use in dogs. In view of the recognized association of megacolon and ureteral dilatation this procedure was

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[11] McLean, D. W. and Fais, O. G.: The use of segments of small intestine as ureters. J. Urol., 68: 190, 1952.

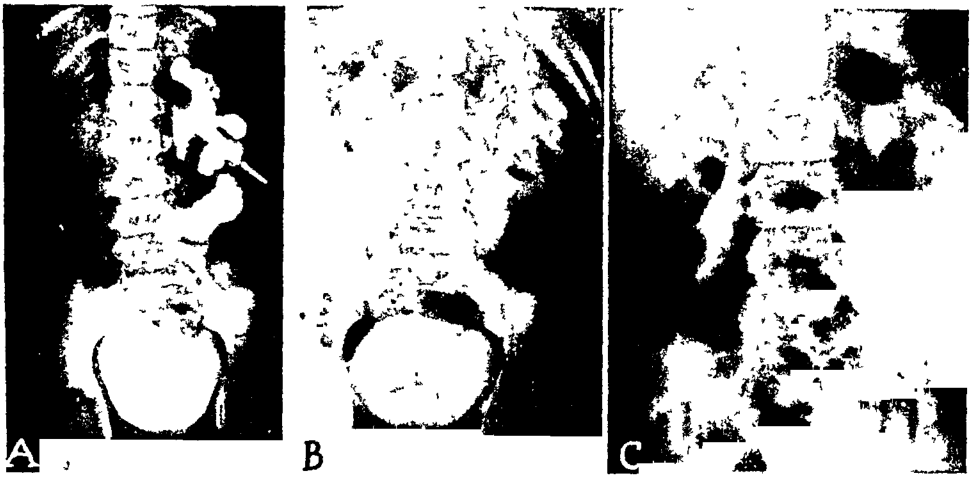

FIG. 2. Case 3. *A*, injection of radio-opaque dye through nephrostomy tube 3 weeks after replacement of left ureter by isolated loop of ileum. *B*, cystogram demonstrating reflux up ileal loop. *C*, excretory urogram 4 months following use of ileal loop to replace left ureter.

undertaken after x-ray investigation had excluded any intestinal abnormality. At a point about 18 inches from the ileocaecal valve a loop of ileum and mesentery was isolated. This loop was swung across in front of the colon and anastomosed to the renal pelvis and bladder, after the removal of the affected ureter. Active peristalsis was again observed during the manipulation of the ureter. The operation was completed by the insertion of a nephrostomy drainage tube.

Following this surgery the patient's general condition improved steadily and although her urine remained infected she became asymptomatic and the pain and tenderness in the left costovertebral angle subsided. During the first few weeks the urine contained varying amounts of mucus from the transplanted intestine but this gradually subsided and is now completely absent.

Two weeks after operation radio-opaque dye injected through the nephrostomy tube and observed during fluoroscopic screening was seen to pass rapidly from renal pelvis to bladder (fig. 2, *A*). A cystogram also made at this time showed that reflux occurred up the intestinal loop (fig. 2, *B*). However, as drainage from the renal pelvis was so efficient the nephrostomy tube was removed 21 days after operation and the wound healed rapidly.

The initial satisfactory progress that this child made has been maintained and when last seen 4 months after operation her urine contained only a few pus cells with an occasional bacillus when examined microscopically.

Commentary on case 3: Several writers on this subject (MacMyn[12], Hurst and Gaymer-Jones[13], Swenson and associates[14] and Lewis and Kimbrough[15]) have drawn comparisons between primary megalo-ureter and congenital megacolon,

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[12] MacMyn, D J On dilatation of the ureters and hydronephrosis in childhood. Brit. J. Urol., **1**: 150, 1929

[13] Hurst, A F and Gaymer-Jones, J : A case of megalo-ureter due to achalasia of the ureterovesical sphincter. Brit. J. Urol., **3**: 43, 1931.

[14] Swenson, O , MacMahon, H. E., Jaques, W E. and Campbell, J. S. A new concept of the etiology of megaloureters New Eng J. Med., **246**: 41, 1952

[15] Lewis, E. L. and Kimbrough, J. C.: Megalo-ureter New concept in treatment. South. Med. J., **45**: 171, 1952

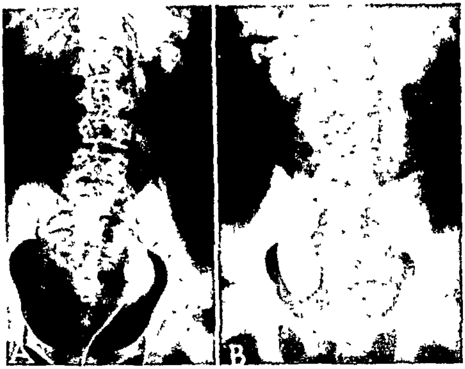

FIG. 3. Case 4. Retrograde pyelograms (1931) showing bilateral megalo-ureter.

and indeed the two conditions are sometimes co-existent (Moore and Lawrence[16]). In this case and in case 2 it was noted at operation that the dilated portion of ureter had inherent contractibility when stimulated and terminated from 2 to 4 cm. from the ureterovesical junction, these lower few centimeters of ureter being of normal size. Such an appearance certainly seems to suggest an analogy to the dilated and hypertrophic colon proximal to a narrow section of bowel which Swenson and others[17, 18] have shown to be devoid of parasympathetic nerve supply in congenital megacolon. Kimbrough[15] reports encouragingly on the results of resection of this normal appearing segment of ureter and vesical re-implantation of the dilated ureter. It has been our experience, however, that such an operation produced no improvement in the degree of megalo-ureter in the two cases in which it was employed.

In this case excision of the narrower portion of ureter and re-implantation into the bladder allowed ureteral reflux of urine which had not been present prior to operation. This appeared to initiate a series of severe episodes of ascending infection and pyelonephritis. It is possible that such reflux might be prevented by allowing a short segment of ureter to lie free in the bladder as practiced by Kimbrough who considers that such a procedure is helpful in preventing this complication.

The use of an isolated loop of intestine to replace the ureter undoubtedly improved the child's condition symptomatically and the recurrent episodes of pyelonephritis ceased. Up to the present time the result of this operation appears very satisfactory, but a longer period of observation will be necessary before final evaluation of such a procedure can be made. It may be pertinent to remark on the possibilities of such an operation in the treatment of other conditions in which replacement of a ureter is necessary.

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[16] Moore, T. C. and Lawrence, E. A.: Congenital malformation of the rectum and anus. Surg Gynec. & Obst., 95: 281, 1952.

[17] Swanson, O , [illegible] I.: Hirschsprung's disease: New concept of etiology. Ne [illegible]

[18] Bodian, M. an [illegible] disease: A new concept. Proc. Roy. Soc. Med., 42: 225, 1 [illegible]

Case 4. M. E., an unmarried 33 year old woman, has been observed at University Hospital since she was nine, when her mother stated that she had had episodes of fever accompanied by flank pain since the age of two. Cystoscopy revealed an inflamed but otherwise normal appearing right ureteral orifice and a normal left ureteral orifice. Catheterization of both ureters was easily performed and there was no evidence of obstruction. The specimens of urine obtained from the ureters were heavily loaded with pus cells and bacilli. Pyeloureterograms (fig. 3, *A* and *B*) made at this time revealed bilateral ureteral dilatation but the renal calyceal systems did not show a commensurate degree of deformity although hydronephrosis was present.

At intervals for the next 6 years lavage of both ureters was carried out and with this treatment she remained in good health and remarkably free from symptoms, and the intervals during which the bladder urine was free from infection became increasingly longer.

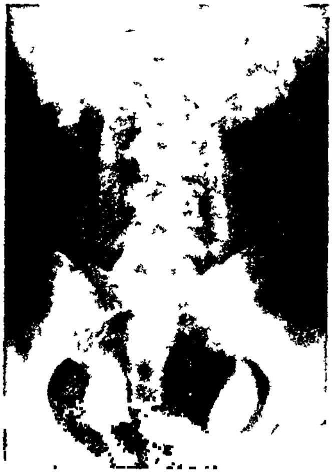

FIG. 4. Case 4. Retrograde pyelograms (1948). In spite of persistence of bilateral megaloureter, patient's renal function remains good, she has uninfected urine and is leading an active life No operation was performed

In 1935, however, when the patient was aged 15, severe urinary tract infection recurred accompanied by bilateral flank pain radiating to the lower abdomen. It was noted that these bouts of infection coincided with her menstrual periods. Owing to the increasing severity of the attacks and their persistent association with menstruation, an x-ray sterilization was considered advisable. This produced a dramatic amelioration of her urinary symptoms. The improvement was maintained and she was well until 1948 when menstruation re-commenced and pain recurred, to be relieved once again when x-ray therapy terminated her periods.

Since this time she has remained entirely free from symptoms and has led an active and healthy life as a teacher. It is noteworthy that her urinary tract infection was promptly cleared on the institution of treatment with sulfonamide drugs, and has not returned. Her ureterograms made at intervals since 1929 show that the degree of ureteral dilatation has not materially changed, nor has there been evidence of increasing hydronephrosis (fig. 4). Recent renal function tests show that the phenolsulfonphthalein clearance was 58 per cent in 2 hours.

Commentary on case 1. The satisfactory result in this case from conservative management adds weight to the doubts cast on the value of any surgical interference in these cases It must be noted again, however, that the dilatation of her ureters has persisted unchanged throughout the course of our observation

A further point of interest in this case is the manner in which the infection of the urine seemed to be closely associated with menstruation and was cleared by an artificial menopause Such an association may favor the possibility of an hormonal factor in the etiology of this condition In this respect also the anatomical relationship of the uterine artery to the lower end of the ureter must not be forgotten

DISCUSSION

At the present time the many theories of the cause of primary megalo ureter are all largely conjectural. With so little understood about the etiology it is not surprising that varied surgical approaches to the problem have been attempted

It had been believed in the past that suprapubic cystostomy alone had, in some instances, resulted in decrease in the size of the ureters In the light of present knowledge, however, it is probable that those cases in which improvement has been noted, were, in fact, not true primary megalo-ureters, but cases in which faulty vesical function was present Neither suprapubic cystostomy nor continuous bladder drainage by catheter has resulted in diminution of ureteral dilatation in any of the cases reported here

Our present investigation has sought an answer to the question of whether the operative procedures in these cases have yielded significant clinical benefits

Operation in all 3 cases was performed in an effort to alleviate the following conditions. gross bilateral ureteral dilatation, infection in the urine, and episodes of sepsis All three of the cases following operation have shown persistence of the ureteral dilatation, and have continued to have infection of the urine Based on the stated criteria one is forced to conclude that results hoped for have not been attained

Compared to these 3 cases the other patient in whom no operation was performed also has dilated ureters, but she is clinically well and has been free from infection for nearly ten years It appears that she has fared better than the others

Our present opinion regarding the management of such cases would be this: the clinician who faces any problem of this sort must focus his attention on excluding evidence of obstructive uropathy which might be amenable to surgical correction It is only when all such factors are found to be lacking that a diagnosis of primary megalo ureter can be established It seems that renal function remains surprisingly good in these cases, and that the prognosis need not be as pessimistic as the degree of ureteral dilatation would at first suggest

Perhaps in this particular type of case it might be better to focus our therapeutic efforts along conservative antibacterial avenues and be less concerned with correction of ureteral dilatation

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THE INTRAPSOAS TRANSPLANT OF MEGALO-URETER

HJALMAR E. CARLSON

In congenital megalo-ureter the etiology is as yet unknown but has been described as due to 1) neurogenic causes, 2) obstructive causes, or 3) due to developmental arrest. Whatever the basic cause may be there is some type of neuromuscular dysfunction involved. When the ureters are involved in neuromuscular dysfunction usually both ureters are affected, and usually equally, although I have seen a number of cases where only one ureter was involved. Of the 12 cases I have seen, few have had any actual obstruction at the ureterovesical orifice and catheters can readily be passed. Some cases may have vesical neck contracture or strictures but in most cases there is no such obstruction.

In the treatment of megalo-ureter ureteral meatotomies prehaps have been of some value even though there is no actual stricture. Transurethral resection of the vesical neck to facilitate drainage with or without contracture of the bladder neck has been reported favorably. Re-implantation of the ureter into the bladder to create a large ostium either with or without the pull-through technique has been reported to be of value. I have seen some very good results with this method. The excision of the redundant ureter, with end-to-end anastomosis and preservation of the ureterovesical orifice has its advocates. Permanent ureterostomies and permanent nephrostomies have been performed. Even with this approach the disease is usually although not always progressive, and death is the end-result from pyelonephritis, uremia, hypertension and coronary disease. In an attempt to stimulate the emptying of the megalo-ureter I reasoned that perhaps the voluntary muscles, if they could be brought into play, might be of some value. In some way perhaps then the dysfunction could be overcome or at least arrested. The psoas muscle lying along the spine and just beneath the ureter seemed the most logical muscle to use, inasmuch as it is accessible from a point above the kidney as well as down into the pelvis. The number of cases of megalo-ureter seen by the average urologist is not great, and suitable cases are not always forthcoming, so I am therefore only able to report on 2 cases in which the ureter has been implanted within the psoas muscle; however, I would like to present the technique to you since only by observations of several can the procedure be truly evaluated.

The technique of the operation is simple (figs. 1 and 2). The patient is placed on his side with the table broken in typical kidney position. The incision is extended well into the lower quadrant. Since the patients are children the bladder lies relatively high and the juxtamural ureter is therefore not difficult to visualize. The dilated ureter with its various tortuosities and adhesions is freed from the kidney to the bladder. With the additional length gained from freeing of the adhesions it can then be readily transplanted into a trough in the psoas muscle. This trough should extend from a point just below the renal pelvis to a point just proximal to the bladder, and is made as deep as possible. The psoas muscle

Read at annual meeting, American Urological Association, St. Louis, Mo. May 14, 1953.

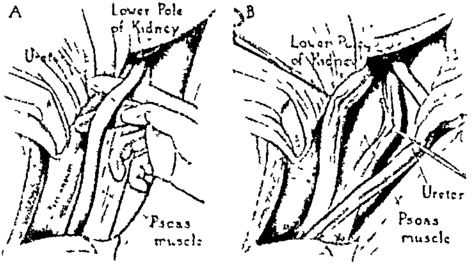

FIG. 1. *A*, ureter is freed from kidney to bladder. *B*, trough in psoas muscle is prepared.

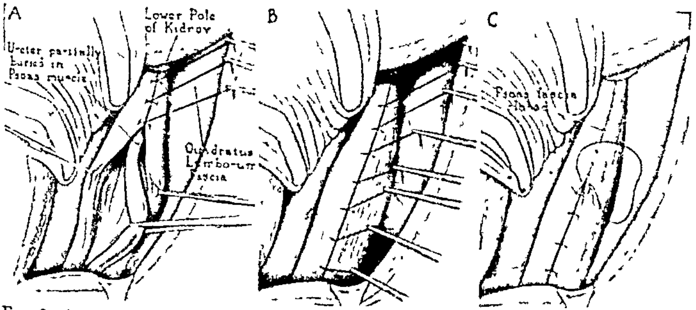
A
Lower Pole of Kidney
Ureter partially buried in Psoas muscle
Quadratus Lumborum fascia
B
C
Psoas fascia closed

FIG. 2. *A*, ureter is buried within psoas muscle with interrupted sutures of chromic catgut. *B*, almost entire ureter can be buried. *C*, psoas fascia is closed and fascial nephropexy then done.

is approximated over the ureter with interrupted chromic catgut sutures and the psoas fascia with a running catgut suture. The perirenal fascia is used to suspend the kidney to prevent angulation of the ureteropelvic junction.

CASE REPORTS

Case 1. M. 39148, E. S., a girl, aged 1 year, was first seen in January 1949 because of urinary incontinence and apparent pain on urination. There was a history of a common anal and vaginal opening at birth and this had been previously corrected on the gynecology service. On cystoscopic examination, January 28, 1949, bilateral hydro-ureters were found. Sulfonamides and antibiotics relieved her symptoms. Blood chemistry studies were normal. Approximately one year later, on December 9, 1949, recheck retrograde pyelograms (fig. 3) showed some increased dilation of the ureters, and there was still further increase on pyelograms on October 27, 1950 (fig. 3). On December 1, 1950, the right ureter was freed from the kidney to the pelvic brim and loosely placed in the psoas trough prepared for it. The ureter was found to be approximately 1 cm. in diameter and, as is usually true, it is always larger and more tortuous at operation than on the x-ray. Five interrupted chromic No. 1 catgut sutures were loosely

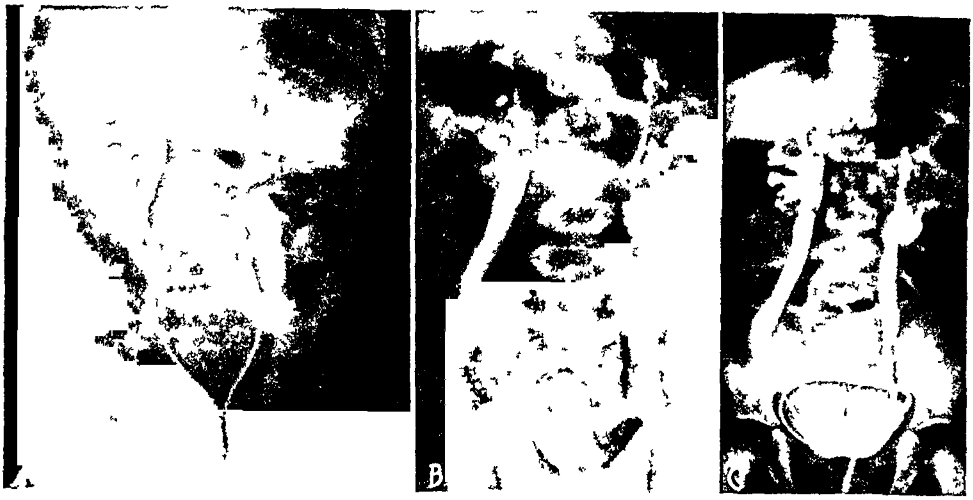

FIG. 3. Case 1 *A*, preoperative pyelogram 2 years before operation. *B*, preoperative pyelogram 1 year before operation. *C*, preoperative pyelogram.

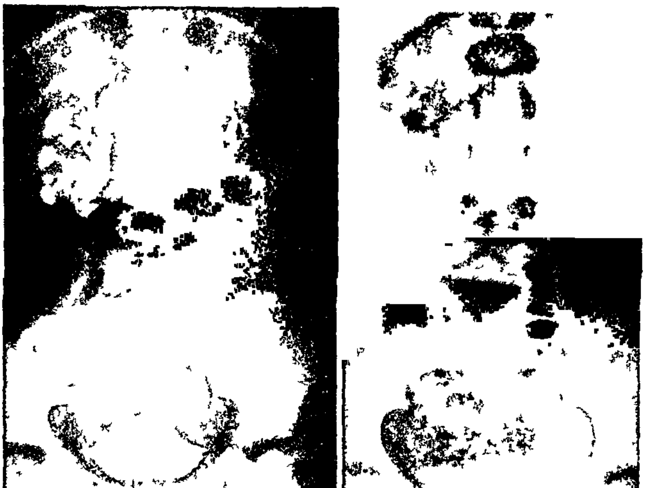

FIG. 4. Case 1. *A*, pyelogram 2 months after transplantation of right megalo-ureter into psoas muscle *B*, excretory urogram 2½ years after operation

approximated over the ureter, and the psoas fascia closed with a running suture of plain catgut. On January 5, 1951, a retrograde pyelogram was made and diminution in the size of the right ureter was observed. Excretory urograms were unsatisfactory because of poor renal function. On March 17, 1953, an excretory urogram disclosed some increased dilation of the right ureter (fig. 4). Urine examination was negative for albumin and microscopically there were 5 to 8 pus cells per high power field. The blood chemistry showed nonprotein nitrogen 25 per cent, CO_2 42 volume per cent, and chlorides 552 mg. It was my feeling that had the ureter been buried in a more satisfactory manner a more permanent result would have been obtained.

Case 2. M. 42661, B. H., a girl, aged 9 years, was seen because of enuresis.

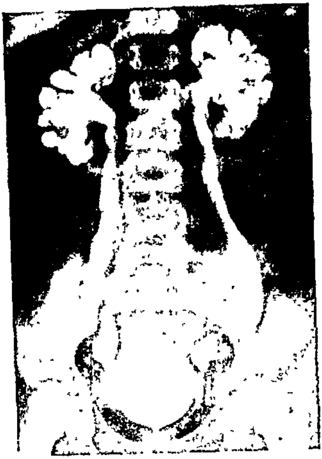

FIG. 5. Case 2. Preoperative pyelogram

Urine examination showed 10–15 white blood cells per cubic millimeter but it was otherwise negative. An excretory urogram taken August 13, 1952 showed no renal function. Retrograde pyelograms were taken August 14, 1952, and bilateral hydro-ureters of equal extent were demonstrated (fig. 5). On August 29, 1952, an intrapsoas transplant of the left ureter was performed. On this occasion the psoas trough was both deeper and more extensive than in the previous case and extended from the kidney to within one or two centimeters of the bladder. Suturing was also more complete and the psoas muscle was tightly rather than loosely closed over the ureter. As previously, the ureter was greatly dilated and approximated 2 cm. in diameter. The psoas fascia was closed after approximating the muscle with No. 1 interrupted chromic catgut sutures. The nonprotein nitrogen, which had been 51 prior to operation, rose after operation to 83, but 2 weeks postoperatively, on September 13, 1952, it was 56 mg. per 100 cc. Blood chemistry studies made subsequently have shown some variations but on the last study, March 20, 1953, the nonprotein nitrogen was 45. Part of this variation no doubt can be explained by the megacolon, which was also found. Retrograde pyelograms were made on the operative side October 13, 1952, and on March 13, 1953, an excretory urogram was taken (fig. 6). Fortunately sufficient function was present so that the kidneys and ureters could be visualized. The advantages of excretory urograms in a study of this type are of great importance. According to the Department of Roentgenology, there was a definite diminution in the size of the kidney and ureter on the operated side as compared with the unoperated side.

Both children feel fine. In the first instance it is extremely difficult to secure follow-up because of the feeling of well being, and in the second case the sub-

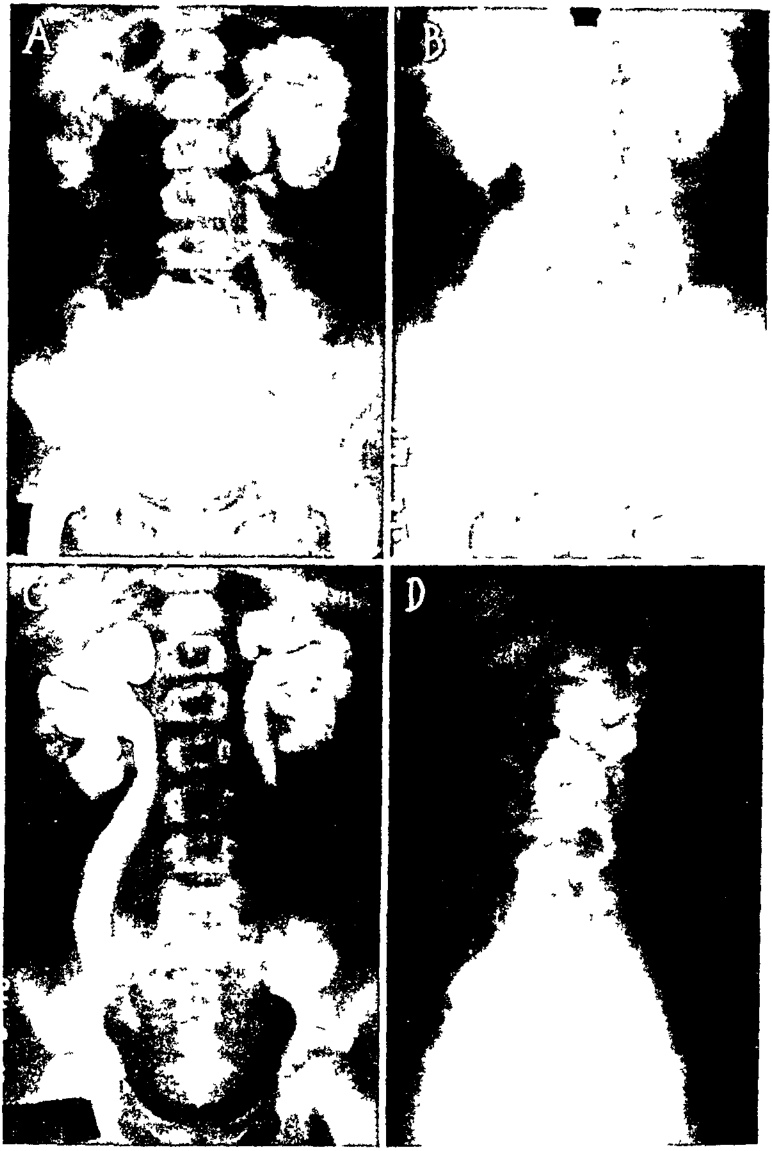

FIG. 6. *A*, pyelogram 6 weeks after intrapsoas transplant of left megalo-ureter. *B*, excretory urogram 6 months after operation. *C*, retrograde pyelogram 6 months after operation. *D*, lateral pyelogram showing position of ureter.

jective improvement in the child has made the parents so extremely grateful that follow-up should be no problem.

SUMMARY

A new operation for megalo-ureter is presented consisting of the transplantation of the dilated ureter into a trough made by splitting the psoas muscle. The activity of the psoas muscle in daily living should stimulate the ureter to improved function.

The trough should be both as deep and as long as possible and should extend from the renal pelvis to within one or two centimeters of the bladder.

The psoas muscle should be tightly closed over the ureter with interrupted sutures of chromic catgut and the psoas fascia approximated. The kidney should be suspended to prevent angulation of the ureteropelvic junction.

Two children, both girls, are presented with bilateral megalo-ureters, each of approximately the same grade on either side. In each instance one side was operated upon and the other side was left as a control.

The results of the operation may be regarded to have some merit, although conclusive results have yet to be obtained and further cases are needed.

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TABLE 1—*Continued*

CONTRACTION	RELAXATION	BY STIMULATION OF	ANIMAL	AUTHOR[1]	DATE
Base of Bladder		Hypogastric nerves	Dog	Elliott Fagge	1907 1902
			Cat, Dog	Debaisieux[7]	1912
		Distal cut end hypogastric nerves	Cat	Dale Langley & Anderson[7]	1906 1894
			Dog	Hanč	1898
Base of Bladder →	Bladder[5]	Hypogastric nerves	Cat	Dale Edmunds & Roth Lewandowsky	1906 1920 1900
		Distal cut end hypogastric nerves	Cat	Barrington Elliott	1915 1907
			Cat, Dog	Langley & Anderson	1895
		Anterior roots of lumbar spinal nerves	Cat, Dog	Langley & Anderson	1895

cut ends. Courtade and Guyon (1896) believed that the contraction which resulted from excitation of intact hypogastric nerves was solely a reflex phenomenon. Elliott ('07), and Griffiths (1894) always sectioned the hypogastric nerves and stimulated their distal cut ends to avoid reflex changes. Stewart (1899a, 1899b) observed no difference in unilateral stimulation of an intact or sectioned nerve except that excitation of the former caused a passive bulging on the contralateral side. The majority of the workers, among them Kuntz and Saccomanno ('44), and Langley and Anderson (1894, 1895) found no essential difference in the response obtained from stimulation of intact nerves or of their peripheral cut ends. See table 1.

Most workers believe that a hypogastric nerve supplies only the corresponding side of the bladder. A strictly unilateral response was observed by Griffiths (1894), and Stewart (1899a), upon excitation of the distal cut end of a hypogastric nerve. See table 1. Sherrington (1892) obtained a similar result following stimulation of anterior lumbar roots of spinal nerves. Debaisieux ('12), MacDonald and McCrea ('30), and Langley and Anderson (1894) reported a slight contraction on the contralateral side in addition to the usual homolateral response. After an extensive review of the literature Gruber ('33) came to the conclusion that the bladder response evoked on excitation of the distal cut end of a hypogastric nerve was limited in its effect to the corresponding half of the viscus and affected equally all portions of the detrusor muscle.

It is apparent that there is need for more precisely determined information on the pattern of response evoked by activity of the sympathetic outflow.

Previously, using the method devised for measuring the regional activity of the bladder (Hegre and Ingersoll, '49), it was found that all regions of the bladder participate in the diphasic response following bilateral stimulation of the sympathetic outflow and, in addition, that all portions of the viscus exhibit spontaneous activity (Ingersoll and Hegre, '51). The present study was undertaken to ascertain the behavior of the detrusor muscle in response to unilateral stimulation of hypogastric nerves.

METHODS

Adult cats, anesthetized with 20 mg. Dial (Ciba) and 50 mg. chloralosane (per kg., i. p.), were used. Following a midventral abdominal incision to expose the hypogastric and pelvic nerves the bladder was rotated so that the posterior surface was uppermost. On this surface were placed small squares of white adhesive paper each bearing a small black spot in its center. The paper squares were arranged so as to divide this surface into quadrants and segments (fig. 1). By means of a Ciné-Kodak Special 16 mm. camera, mounted above the bladder, photographs were taken at 1 sec. intervals during the course of each observation. Subsequently, by projecting the film onto suitable paper, measurements were made and the results plotted of the activity taking place per unit length of muscle in each segment during each sec. of observation. In addition, a kymograph record was kept of the total bladder response under conditions of constant pressure (Hegre and Ingersoll, '49). A square wave stimulator (Grass) was used in all experiments with the instrument set to discharge at a frequency of 20–30 per sec., a 2 msec. delay and at a duration rate of 5 msec.

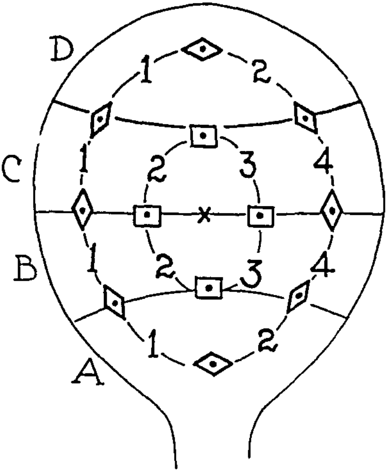

Fig. 1 Schematic drawing of exposed surface of bladder showing location of quadrants and segments

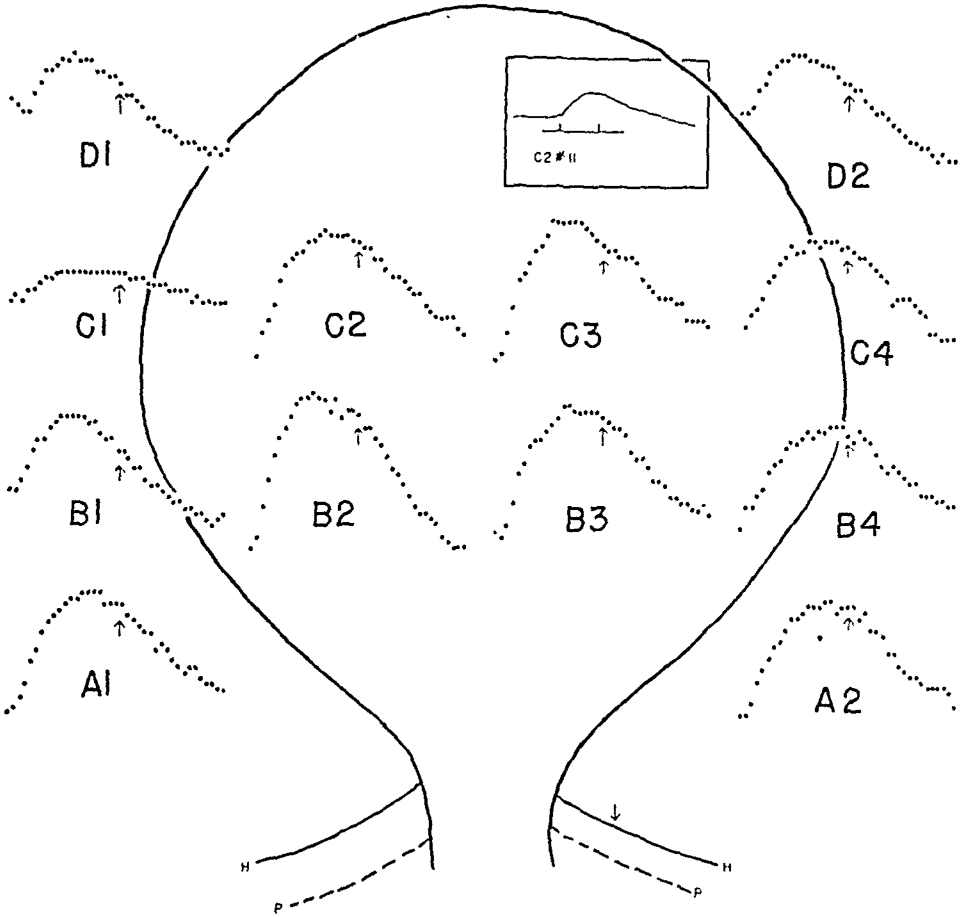

FIG. 2. *Bladder responses in cat 2, exp. 11. Unilateral stimulation of a hypogastric nerve with all nerves to the bladder intact. Intravesical pressure held constant at 14 cm. water.*

Figures 2–7 are graphic records of muscle activity taking place in each bladder segment in response to unilateral stimulation of hypogastric nerves. Each circle represents activity taking place during each second of observation. Onset of stimulation coincides with first circle of each curve while cessation of stimulation is indicated by an upward pointing arrow (except in fig. 7, upper curves, where period of stimulation was 59 sec.). A downward pointing arrow indicates side of bladder stimulated. A cross-bar through a nerve indicates section of that nerve. Insert: kymograph record of each observation, together with the time of stimulation. Abbreviations: H, hypogastric nerve; P, pelvic nerve; A1, A2, B1, etc., bladder segments.

RESULTS

1. *Effect of unilateral stimulation of hypogastric nerves with all nerves to the bladder intact.* Unilateral stimulation resulted in a prompt diphasic response of the detrusor muscle on the corresponding side (figs. 2, 3, 4). The period of initial contraction lasted from 8 to 15 sec. and was followed immediately by relaxation in the same regions.

On the contralateral side several types of responses occurred. The one most frequently observed was similar to that recorded on the stimulated side. In some instances the initial contraction was very brief and was followed by a prolonged relaxation (fig. 3, D1, upper curve; fig. 4, B1, upper curve). Another type of response had a latent period of 1 to 3 sec. before the onset of contraction (fig. 3,

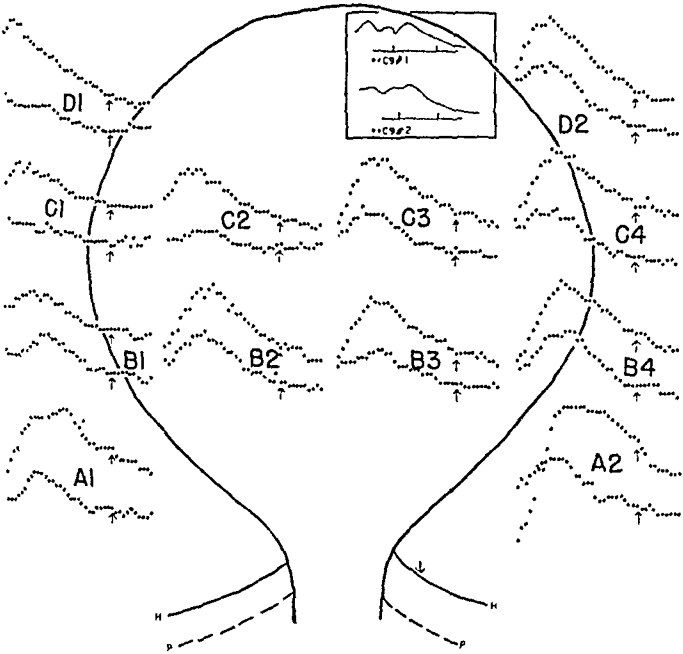

Fig. 3. Bladder responses in cat 9. Unilateral stimulation of hypogastric nerves with all nerves to the bladder intact. Upper curves, closed circles (exp. 1), right hypogastric nerve stimulated; lower curves, open circles (exp. 2), left hypogastric nerve stimulated. Intravesical pressure held constant at 16 cm. water.

A1, lower curve; fig. 4, C1, upper curve and B2, lower curve). In some regions the detrusor muscle relaxed during this period of initial delay (fig. 2, D1; fig. 4, C2, upper curve). In the remainder of the responses relaxation of the detrusor was pronounced and occurred without the usual initial contraction (fig. 3, C1, D1, lower curve; fig. 4, B1, C1, C2, D1, lower curve).

The amount of initial contraction per unit length of muscle, following unilateral stimulation of intact nerves, showed considerable variation. In one experiment (fig. 8, C2 No. 11) the average amount of contraction in the homolateral and contralateral halves of the viscus was about equal, while in the other studies in this series (fig. 8) marked differences were evident. In two observations from cat 9 stimulation of the right hypogastric nerve (C9 No. 1) elicited a greater response than when the left nerve was excited (C9 No. 2). Similar studies in cat 4 (C4 No. 2, C4 No. 4) also evoked contrasting reactions. Relaxation without previous contraction was a notable feature on the contralateral side in two of these bladder studies (C9 No. 2; C4 No. 4).

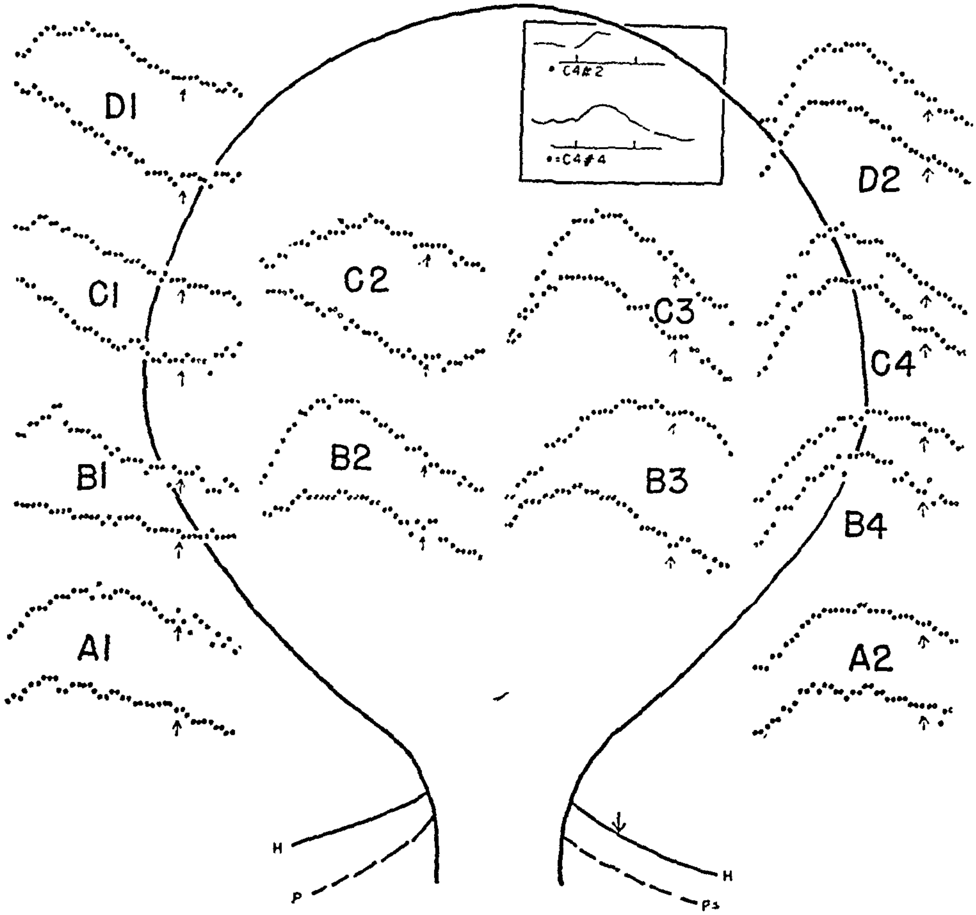

FIG. 4. Bladder responses in cat 4. Unilateral stimulation of hypogastric nerves with all nerves to the bladder intact. In upper curves, closed circles (exp. 2) left hypogastric nerve stimulated; in lower curves, open circles (exp. 4) right hypogastric nerve stimulated. Intravesical pressure held constant at 27 cm. water.

2. *Effect of unilateral stimulation of intact hypogastric nerves after section of the pelvic nerves.* Unilateral stimulation of an intact hypogastric nerve following section of the pelvic nerves gave a prompt and unusually vigorous response in all regions of the corresponding half of the viscus (fig. 5). On the opposite side similar responses were noted in segments A1, D1, B2, while in the other areas contraction occurred after a short latent period. The amount of contraction per unit length of muscle was considerably greater on the stimulated side than on the opposite side (fig. 9, C9 No. 11).

3. *Effect of unilateral stimulation of the distal cut end of a hypogastric nerve with the opposite hypogastric nerve intact and with the pelvic nerves sectioned.* The response on the stimulated side (fig. 6) was a prompt contraction followed by relaxation. On the opposite side all portions of the detrusor muscle exhibited an initial contraction which was followed by relaxation in the same regions but most of the responses were weak or were delayed 1 to 3 sec.

The average amount of contraction per unit length of muscle was much greater on the stimulated side than on the opposite side (fig. 9, C9 No. 13).

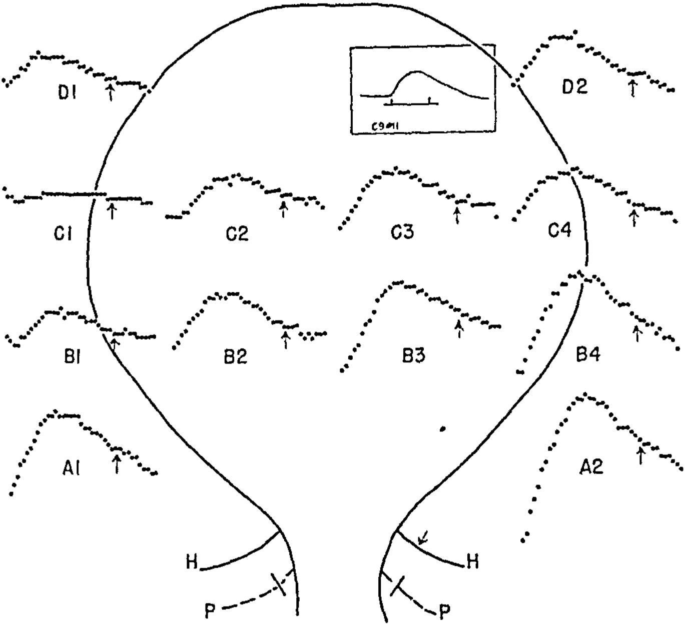

FIG 5 Bladder responses in cat 9, exp 11 Unilateral stimulation of right hypogastric nerve with pelvic nerves sectioned All hypogastric nerves intact Intravesical pressure held constant at 11 cm water

4 *Effect of unilateral stimulation of the distal cut end of a hypogastric nerve with the opposite hypogastric nerve and the pelvic nerves sectioned* The two studies (fig 7) are from the same cat and differ from each other only in the side stimulated (right nerve, C9 No 19, left nerve, C9 No 16) In both observations contraction occurred in all homolateral and in many contralateral segments This response was often delayed or was preceded by an initial relaxation on the contralateral side

The amount of contraction per unit length of muscle following stimulation of the distal cut end of the left hypogastric nerve (fig 9, C9 No 16) was about the same on both sides of the bladder Stimulation of the distal cut end of the right hypogastric nerve (fig 9, C9 No 19), however, evoked a much greater contraction on the stimulated side than on the opposite side and, in addition, the overall contraction was more vigorous when compared to stimulation of the left nerve

DISCUSSION

Data have been presented showing that unilateral stimulation of hypogastric nerves elicited responses, not only on the corresponding side, but on the opposite

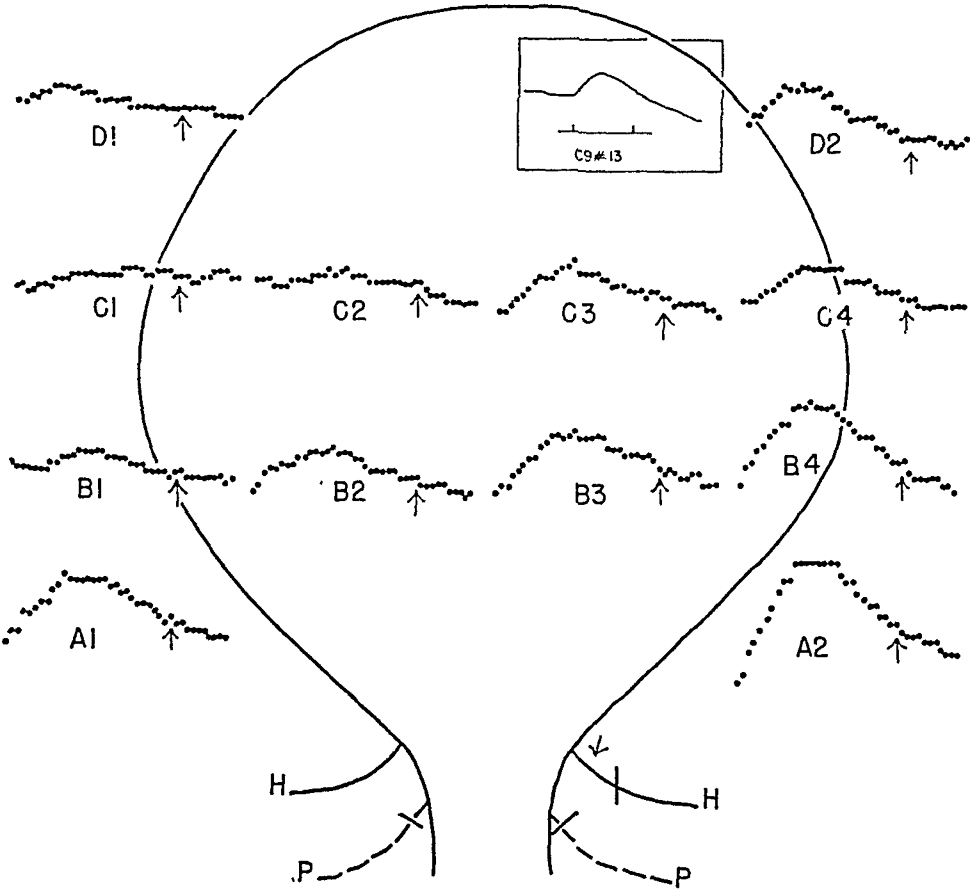

FIG. 6. Bladder responses in cat 9, exp. 13. Unilateral stimulation of distal cut end of right hypogastric nerve with pelvic nerves sectioned. Left hypogastric nerve intact. Intravesical pressure held constant at 11 cm. water.

side of the bladder as well. On the stimulated side there always was a reasonably prompt contraction of the detrusor muscle which was followed usually by relaxation in the same regions. No particular area on the stimulated side could be said to be more active than any other region.

On the contralateral side of the viscus unilateral stimulation evoked more than one type of response. Slightly over half were similar to those observed on the stimulated side. In some regions, especially near the fundus, the contractions were of extremely short duration and were usually followed by prolonged relaxation. Another type of response recorded from the contralateral side had a latent period of from 1 to 4 sec. before the onset of contraction. As a rule, the contraction when it appeared was vigorous and was followed by the customary relaxation. Sectioning of the nerves and stimulation of their distal cut ends had a tendency to delay the onset of contraction. In a few regions the initial contraction was preceded by a very brief relaxation. In other areas this relaxation persisted throughout the period of stimulation.

The amount of contraction per unit length of muscle varied within wide limits in the same and different bladder studies. In one series of observations from the

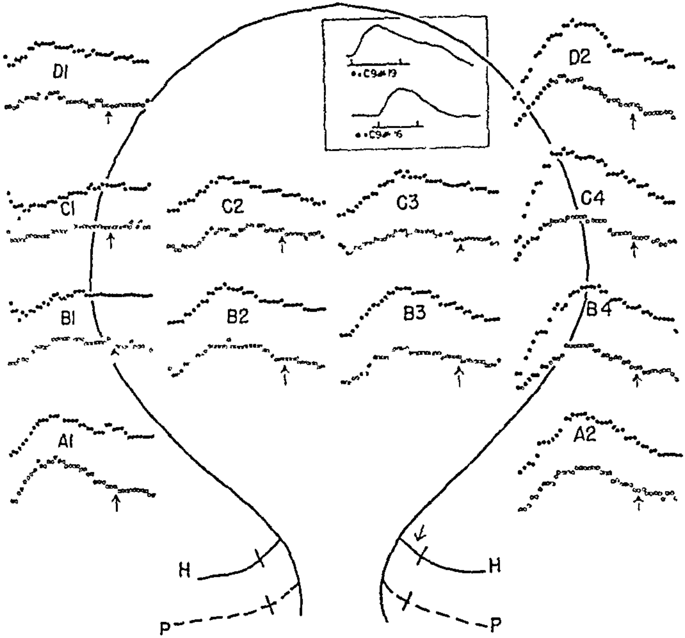

FIG 7 Bladder responses in cat 9 Unilateral stimulation of distal cut end of left hypogastric nerve in exp 16 (lower curves, open circles), and of distal cut end of right hypogastric nerve in exp 19 (upper curves, closed circles) Pelvic nerves sectioned Intravesical pressure held constant at 11 cm water

same cat (C9) stimulation of the right hypogastric nerves regularly elicited a greater contraction, in both halves of the viscus, than stimulation of the hypogastric nerves on the left side This held true following excitation of intact nerves or of their peripheral cut ends In two studies from another cat (C4) similar results were recorded In all of the studies, irrespective of the side stimulated, the average amount of contraction on the homolateral side always exceeded, though sometimes only slightly, the average amount of contraction obtained from the contralateral side The least responsive areas in any single observation were always on the contralateral side, generally along the lateral margin and adjacent to, or within, the fundic portion of the viscus

One factor which was thought by many workers to influence the amount of contraction and subsequent relaxation was the intravesical pressure at the onset of stimulation McCrea and MacDonald ('34) regularly elicited inhibition of vesical activity upon stimulation of the hypogastrics at a good level of pressure They, as well as Mellanby and Pratt ('39), found that when the intravesical pressure was low, bladder contractions were obtained According to the latter investigators, if the pressure was then raised and the same stimulus applied, the

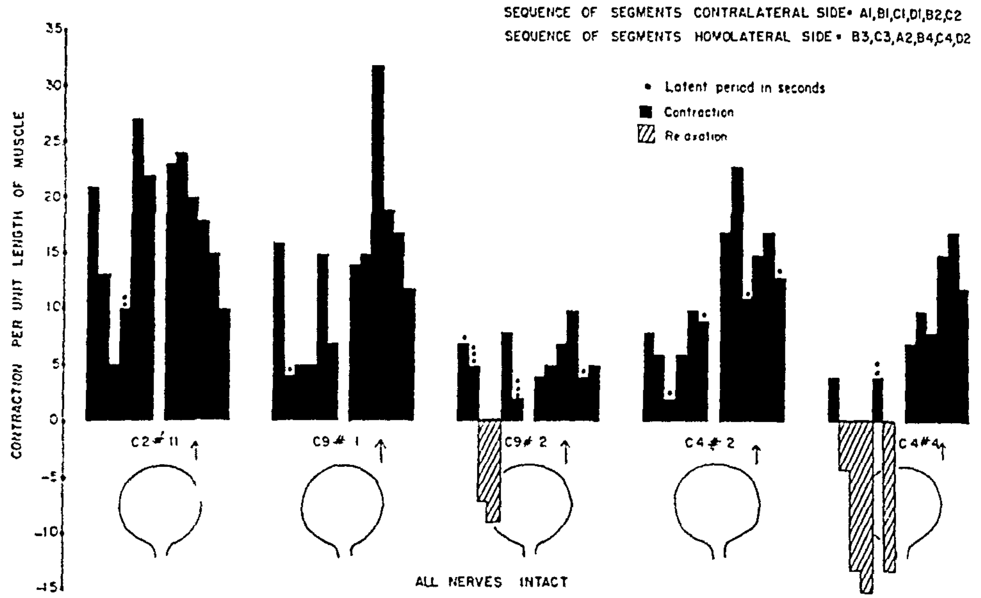

FIG. 8. Graphic representation (prepared from data in figs. 2–4) of the amount of contraction per unit length of muscle in millimeters in response to unilateral stimulation of hypogastric nerves with all nerves to bladder intact. Relaxation following contraction is not shown. Regional activity is grouped into homolateral (indicated by upward pointing arrow) and contralateral blocks. Sequence of segments in each of blocks is from left to right. Abbreviations as before.

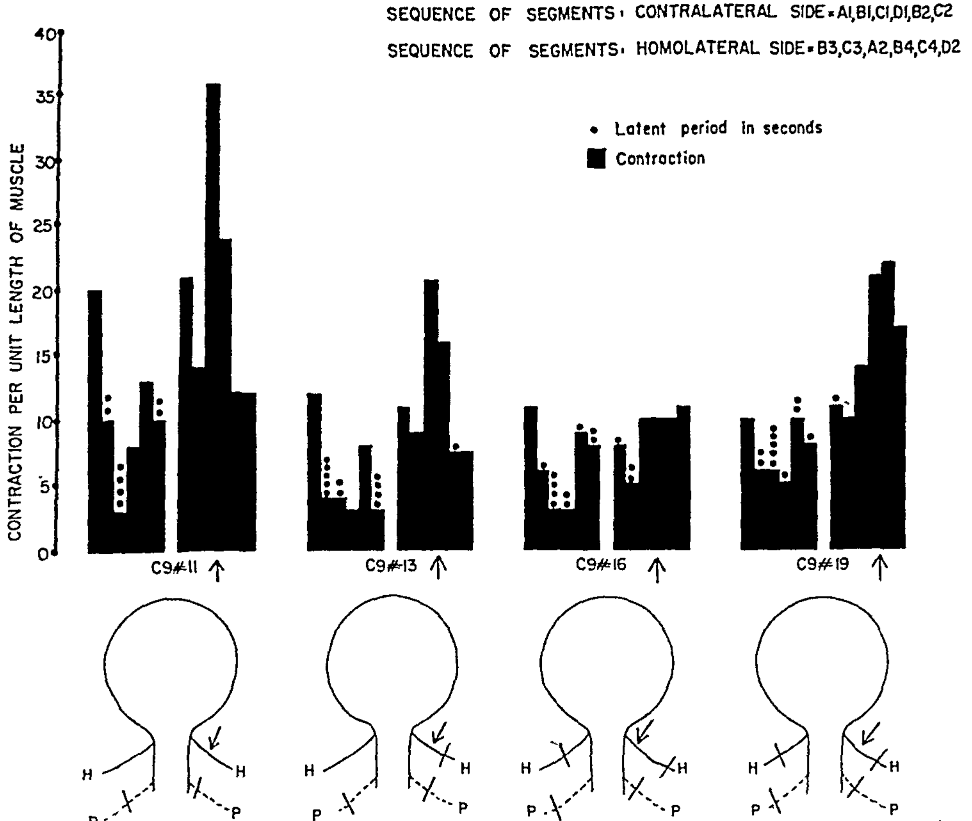

FIG. 9. Graphic representation, prepared from data in figs. 5–7, of amount of contraction per unit length of muscle in millimeters following unilateral stimulation of hypogastric nerves. Relaxation following contraction is not shown. Abbreviations as before.

initial contraction obtained was small and the subsequent relaxation large In our experiments the amount of pressure within the bladder seemed to have little effect upon the amount of contraction and subsequent relaxation but we did obtain marked differences in the amount of contraction by stimulating different sides of the same bladder. In a previous report (Hegre and Ingersoll, '49) evidence was advanced to show that the prestimulatory volume was of greater significance than the intravesical pressure in determining the amount of contraction and resulting relaxation.

The responses which have been obtained from unilateral stimulation of intact nerves and of their distal cut ends indicate a much more extensive bilateral innervation of the detrusor muscle than has been suggested heretofore. It is reasonable to assume from these data that all regions of the viscus are supplied by each hypogastric nerve. However, the richness of the supply is variable, not only to the contralateral side, but to the same side as well.

SUMMARY

Unilateral stimulation of hypogastric nerves always elicited on the corresponding side a prompt contraction of all portions of the detrusor muscle which was followed immediately by relaxation in the same regions.

On the opposite side slightly over one-half of the responses, following unilateral stimulation of hypogastric nerves, were similar to those observed on the stimulated side. Another group of responses had a latent period of from 1 to 4 sec before the onset of contraction. Sectioning of the nerves and excitation of their distal cut ends had a tendency to lengthen the latent period. In the remainder of the responses elicited from the contralateral side the initial reaction was one of relaxation. In some regions this was followed by contraction and subsequent relaxation; in others, relaxation was the only response.

The amount of contraction per unit length of muscle in response to unilateral stimulation varied within wide limits in the same and different bladders. Sectioning of the nerves or altering the intravesical pressure did not materially affect the result. The average amount of contraction on the homolateral side always exceeded that obtained from the opposite side The least responsive areas in any single observation were on the contralateral side, generally along the lateral margin and adjacent to or, within, the fundic portion of the bladder.

These studies indicate a much more extensive bilateral innervation of the detrusor muscle by hypogastric nerves than has been previously suggested. All areas of the bladder wall were found to be supplied by each hypogastric nerve but the richness of this innervation was quite variable, especially on the contralateral side, near the lateral margin of the viscus.

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STRIATED MUSCLE FIBERS OF THE VESICAL NECK

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Previous studies[1, 2] dealt with physiologic observations of the vesical neck following pudendal nerve anesthesia[1] and pudendal nerve stimulation.[2] These observations were explained on the basis of anatomical findings of intertwining smooth and striated muscle fibers at the bladder neck as reported in the literature.[3, 4a, b, 5, 6, 7] The purpose of our investigation was to confirm the presence of striated fibers in shavings obtained by transurethral resection, to endoscopically find their location and to examine them for possible pathological changes.

PROCEDURE AND RESULTS

Twenty-one patients were investigated. All but one, who had an epidural abscess, suffered from traumatic lesions of the spinal cord or cauda equina. Fifteen patients had upper motor neuron lesions and six had lower motor neuron lesions. Of the latter group, two patients had a secondary lower motor lesion following a subarachnoid injection of absolute alcohol for the treatment of skeletal spasticity and one had a degenerative lesion of the cord below his original level of T-9. Three patients with levels at C5, C6 and T5, respectively, had incomplete lesions, while the rest had physiological or anatomical transections. The spinal cord level ranged from C6 to L1 and the age from 19–44 years. The time interval between injury and vesical neck resection was from six months to two years in the majority of cases; four patients underwent surgery between 5 and 8 years, respectively.

The Stern-McCarthy and Baumrucker instruments were used for resection. The tissue was retrieved from the bladder neck proximally to the verumontanum.

The strips of resected tissue were submitted to the laboratory in bottles con-

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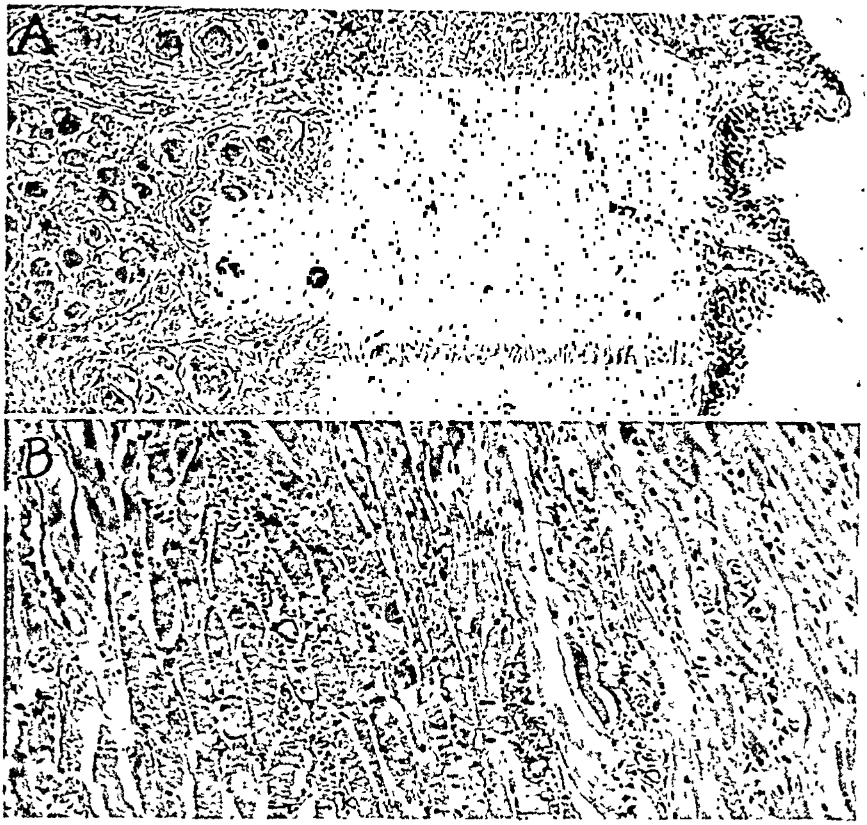

FIG. 1. A, section of vesical neck showing surface of transitional epithelium with underlying stroma, mildly infiltrated by lymphocytes. In deeper portion of section there are bundles of striated muscle, some in close proximity with bands of smooth muscle. B, sections of striated muscle. Mild interstitial edema and small collection of lymphocytes and histiocytes are present.

taining formalin and labeled according to a clock pattern, the code of which was unknown to the pathologist. The strips consisted of from six to approximately forty segments of grayish pink, irregularly smooth and rubbery tissue, the largest segments of which measured 2.0 by 0.5 by 0.5 cm; the amount of tissue varied from 1.8 to 5.2 gm. The tissue was embedded in paraffin and stained with hematoxylin and eosin; where necessary, special stains were used (Van Gieson, Masson, fat).

Microscopically, the segments of tissue consisted for the most part of fibromuscular (smooth muscle) tissue. Many of these strips showed edema and foci of lymphocytes and histiocytes. In segments of vesical neck (fig. 1, *A*) the mucosa consisted of flattened transitional epethelium and the stroma of moderately edematous connective tissue mildly infiltrated with lymphocytes. Underlying bands of smooth muscle were in close proximity to bundles of striated muscle which were lying deep in these strips. In other segments, bundles of striated muscle were separated by edema and collections of polymorphonuclear leukocytes, lymphocytes and histiocytes (fig. 1, *B*). In many areas the striated muscle was undergoing degenerative changes and early fibrosis (fig. 2, *A*). In still other segments, bundles of striated muscle were replaced and surrounded by fibrous tissue (fig. 2, *B*).

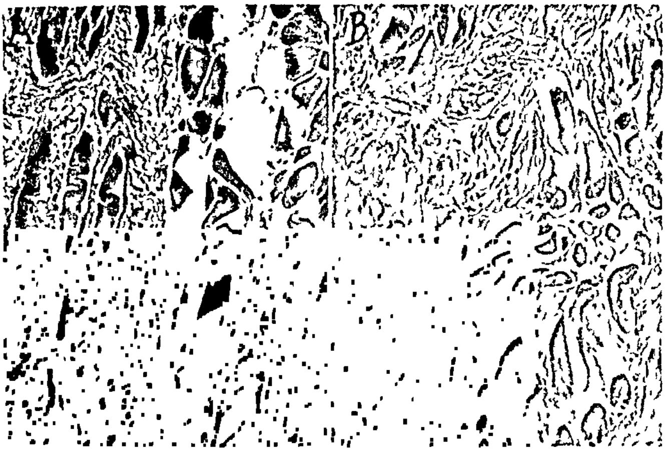

FIG. 2. A, degeneration and mild fibrosis of striated muscle fibers. Artefactual shrinking of muscle substance from sarcolemma. B, bundles of atrophic striated muscle surrounded by bands of replacement fibrous tissue.

In all but two instances, striated fibers were demonstrated in the shavings of the anterior lip between 3 and 9 o'clock, while the posterior lip contained only smooth muscle fibers.

The clinical results of micturition of the 15 patients with upper motor neuron lesions were good in eight and poor in seven cases. In all eight, striated fibers were found in the anterior lip. Of the 7 cases, five did show evidence of resected striated fibers while two did not. Four of these 5 cases had a temporary good result (C7, C7, T7, T11), while the fifth (T1) never responded to the resection. Both cases, whose tissue examination failed to show striated fibers, were quadriplegics.

The results from resection were good in all six cases with lower motor neuron lesions and striated fibers could be demonstrated in all instances.

DISCUSSION

Anatomical descriptions of extension of striated fibers to the vesical neck are reported by Rochet[3] in 1899, Wesson[4a, b] in 1920 and 1950, Young and Wesson[5] in 1921, D'Arcy McCrea[6] in 1926 and Elliot[7] in 1952. These investigations, based upon gross and microscopic examinations of adult and embryologic specimens, indicate that striated fibers of the urethral sphincter mingle with smooth fibers close to the anterior urethral mucosa and contribute to the formation of a functional external bladder "sphincter." It is surprising that striated muscle fibers have not been found in the transurethrally resected tissue. This tissue was variously described by authors as: "fibromuscular prostatic hyperplasia,"[8] "adenofibromatous hyperplasia, inflammatory muscle, smooth muscle,"[9] "hypertrophy of muscle, fibrosis,"[10] "hyperplasia of muscle and inflammatory, adenofibromatous hyperplasia,"[11] and as "fibromuscular tissue, round cell infiltration in fibrous tissue."[12] The failure to mention striated muscles in the shavings is the more astounding as most authors recommend resection along the entire circumference[10, 13, 14, 15, 16, 17] and very few restrict their resection to a small localized area of the bladder neck.[18, 19] Some authors,[8, 14, 20, 21] however, have intentionally attacked the external urethral sphincter distally to the verumontanum by excision or electrofulguration, a procedure which, though purposeful and successful, differs anatomically from our operation.

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The recognition of the physiologic significance of an external bladder "sphincter"[22, 23, 24] led consequently to the endeavor to differentiate malinnervation of this "sphincter" from structural contracture by means of pudendal nerve anesthesia.[1] The previous observation of contraction of the vesical neck on stimulation of the pudendal nerve[2] finds further corroboration by demonstration of striated muscle fibers in the presented slides and confirms the veracity of a hypothesis which was based upon the work done by others.[3, 4a, b, 5, 6] These fibers are closer to the mucosal surface than suspected. They are of necessity innervated by a somatic nerve and consequently the pudendal nerve supplies motorically an area which extends through the anterior and lateral aspects of the prostatic urethra and includes at least the urethral slope of the anterior vesical lip.

Thus the theory of micturition of the adult, based upon roentgenologic observation,[25] receives additional support and the striated urethral sphincter cannot be considered to be a mere auxiliary muscle, because its muscular tone is significant for the respective condition of the detrusor. Since these structures

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receive a reciprocal innervation from the same cord segments, by somatic and autonomic fibers, respectively, the difference of micturition between infant and trained child can be better understood considering that training follows chronologically other manifestations of myelinization, e g , walking

The observed pathological changes of degeneration, inflammation and fibrosis of the striated fibers have a farther reaching functional implication because of the intimate proximity between striated and smooth muscles Fibrosis leads eventually to structural contracture of the vesical neck, which can be corrected by a tenotomy-like procedure, in some cases, especially with lower motor neuron lesion, as little as 0 5 gm of tissue will, if removed, make the difference between retention and voiding Radical transurethral resections with removal of large amounts of tissue (more than 5 0 gm) are unnecessary in patients with spinal cord injuries, since these individuals have notoriously small prostates (except older men with pretraumatic prostatic enlargement) and since it is the vesical neck rather than the prostate which causes the bladder imbalance

In analyzing the results of our treatment in these twenty-one patients, the instability of a cord bladder[19] is again demonstrated in that 4 patients (three with lower and one with upper motor neuron lesions) needed resection, 5, 6 and 8 years, respectively, after injury

As was to be expected according to the rationale of treatment, discussed elsewhere,[19] the results were more favorable in the 6 patients with lower motor neuron lesions than in the fifteen with upper motor neuron lesions However, the continence of patients with lower motor neuron lesions is easily jeopardized, this was the case in one of the six patients after the removal of 5 2 gm of tissue from the entire circumference It should be possible to avoid this condition by a gradual resection, performed in several sessions

Of the 7 patients with upper motor neuron lesions, who did not respond to resection, two were paraplegics and five were quadriplegics Restoration of bladder function in quadriplegics is more difficult to achieve than in paraplegics, even auxiliary procedures fail readily in these patients, such as pudendal neurotomy or neurotripsy, because of the absence of volitional abdominal pressure or the use of hands, essential for bladder emptying after the pelvic floor has been paralyzed Pudendal neurotripsies were done in two paraplegics with good results, in one quadriplegic with an equivocal result, micturition being unreliable, and in another quadriplegic with a poor result Three other quadriplegics underwent pudendal nerve anesthesia but the result was either equivocal or the lesion (in two patients) too incomplete to justify destructive surgery of the pudendal nerves

Our past experience during a five year period with 210 resections in 144 patients has taught us that in many instances a resection of the prominent posterior lip will suffice to restore function, this indicates that the structural contracture remained confined to smooth muscles Only when this operation fails or when upper motor neuron lesions do not respond to pudendal nerve anesthesia, must one assume that additional contracture is caused by striated fibers, this condition then requires an extension of the resection to the anterior lip Extreme caution is advisable in cases with lower motor neuron lesions; not to resect too much is the rule because these patients, who by virtue of their cord lesions tend to show stress incontinence, easily become completely incontinent. Primary complete resection around the entire circumference should be the exception rather than the rule in patients with cord injuries.

Why no striated fibers could be recovered in 2 cases from corresponding places where they were demonstrated in nineteen instances, is not understood. Explanations such as individual varieties or depth changes of the striated fibers, are offered as a mere conjecture.

The significance of striated fibers at the described location may be of interest to the urologist who treats, besides traumatic paraplegics, patients with obstructive uropathies. Incontinence after resection need not be due to direct trauma of the urethral sphincter distally to the verumontanum, but (that muscle) may be indirectly weakened by injury of striated fibers during the resection of the anterior prostatic commissure.

SUMMARY

A systematic histologic examination was done of transurethrally resected tissue from the vesical neck of 21 patients with spinal cord lesions.

This examination showed striated muscle fibers of the anterior circumference of the bladder neck and anterior vesical lip in nineteen of the 21 subjects.

Degeneration, infection and fibrosis were present in these fibers, which are located in close proximity to smooth muscle fibers and in shallow relationship to the mucosa.

The literature of anatomical studies is reviewed.

The significance of the findings is discussed for physiological and pathological bladder function.

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SCHISTOSOMIASIS OF THE URINARY BLADDER: WITH SERIAL BIOPSIES UNDER THERAPY

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Cases of parasitism by the diecious blood fluke of Bilharz, Schistosoma haematobium, have been rarely encountered by physicians practicing in the temperate zone. Modern transportation, however, has shortened the distance between the ancient endemic foci of this parasite, Egypt and adjacent areas, and the rest of the world. It therefore behooves the physicians in noninfected areas to be aware of this exotic disease and to have some knowledge of 1) its clinical and pathologic aspects, 2) diagnostic procedures, and 3) the most effective therapeutic measures.

Some fear has been expressed that this parasite might become endemic in other areas. Since its complex life cycle is dependent upon the existence of suitable molluscan hosts, the geographic distribution of S. haematobium is governed by the presence of certain nonoperculate snails (Bulinus, Physopsis, and possibly Lymnaea) (Belding; Craig and Faust; Faust, 1939; Mackie, et al; Strong), to which it is adapted. These genera of snails, for the most part, are common only in southern Europe, Africa, and western Asia; thus the possibility of extension of this blood fluke to other regions is somewhat remote.

Several other aspects of Schistosoma haematobium infection require comment. Faust (1939) estimates the life of the adult parasite in the human body at about twenty years; moreover, though the adult parasites may be killed with therapy, the pathologic reaction to the ova continues. The symptoms may be somewhat minimal for years, and the cure rate with the available drugs is not high (Cummings; Faust, 1939). These aspects prompt us to report this case.

Since the case reported by Peacock and Voegtlin (1935) is thought to be doubtful by Faust (1939), this apparently represents the first authentic case reported from the State of Washington.

CASE REPORT

A 20 year old white foreign seaman was admitted to the urological service of the U.S.P.H.S. Hospital, Seattle, Washington on August 22, 1952, complaining of bilateral flank pain of 5 months' duration. The pain radiated to the pubic region. During this time, he had an episode of painless hematuria which subsided in a few days. There was no history of injury or passage of calculi. Eight days prior to admission, he had frequency, urgency and dysuria which persisted. Past history revealed that the patient was of Greek extraction, born in Egypt, but had resided in Australia since childhood. Even though working as a seaman for the past 4 years, he presented no history of exposure to infection. The family history was irrelevant. He had the usual childhood diseases with no sequelae and

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had been in relatively good health during young adult life. There had been no operations or injuries. System review failed to reveal any pertinent information.

Blood pressure, temperature, pulse and respiration were within normal limits. The average weight was 176 pounds, but the weight on admission was 144. Part of his weight loss could be explained in that his captain suspected appendicitis and withheld solid foods. Except for lower abdominal tenderness on palpation, the physical examination was normal.

Excretory urograms revealed normal-appearing kidneys. No calculi were identified. Dye excretion was normal on both sides in 5 minutes. The left pelvis showed a somewhat bizarre appearance which was thought to be a normal anatomical variation. There was some dilatation, assuming an "S-shaped curve", of the lower ureter on the left. The dorsal and lumbar vertebrae showed no changes.

On admission the hemogram was within normal limits. The Kahn Standard was negative. The urinalysis was normal. Subsequent microscopic urinalyses showed erythrocytes because of cystoscopies and biopsies of the bladder. Culture of the urine showed no growth. Three 24-hour urines for acid-fast culture were reported as negative on Lowenstein's, Petragnani's and cooked blood agar media. Stool examinations showed an occasional Giardia lamblia cyst.

Eosinophil counts of the blood were made during the course of the disease and treatment. On September 12, 1952, the white count was 8,000/mm. with 16 per cent eosinophils.

Total circulating eosinophil counts* were as follows:

9/12	680/mm.		10/24	600/mm.	
9/13		Fuadin	10/27	481/mm.	
9/17	970/mm.	Fuadin	10/29	375/mm.	
9/19	1054/mm.	Fuadin	10/30	487/mm.	
9/22	1012/mm.	Fuadin	10/31	544/mm.	
9/24	900/mm.	Fuadin	11/5	463/mm.	
9/26	624/mm.	Fuadin	11/7	500/mm.	
10/1	875/mm.	Fuadin	11/10	260/mm.	
10/6	562/mm.	Fuadin	11/12	360/mm.	
10/3	626/mm.	Fuadin	11/14	218/mm.	
10/8	745/mm.	Fuadin	11/18	330/mm.	(Hetrazan)
10/10	533/mm.	Fuadin	11/19	325/mm.	(Hetrazan)
10/13	737/mm.	Fuadin	11/21	231/mm.	(Hetrazan)
10/15	581/mm.	Fuadin	11/24	250/mm.	(Hetrazan)
10/17	678/mm.	Fuadin	11/26	330/mm.	(Hetrazan)
10/18		Fuadin	11/28	206/mm.	(Hetrazan)

Examination of urine for ova and miracidia was negative on September 13, when Fuadin† therapy was instituted. Miracidia were seen on only two days, September 16 and 17 (fig. 1,*A*).

Ova were seen on the two succeeding days, September 18 and 19 (fig. 1, *B*). No parasites were found on September 30, October 2 and 7. A culture of the urine on October 2 revealed Escherichia coli. Daily urinalyses from October 14 through October 23 and October 27 through November 6 failed to demonstrate the parasite. Final urinalysis on November 25 was within normal limits.

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* Normal range in this laboratory, 200–300/mm.

† Winthrop Stearns, 6 per cent stibophen.

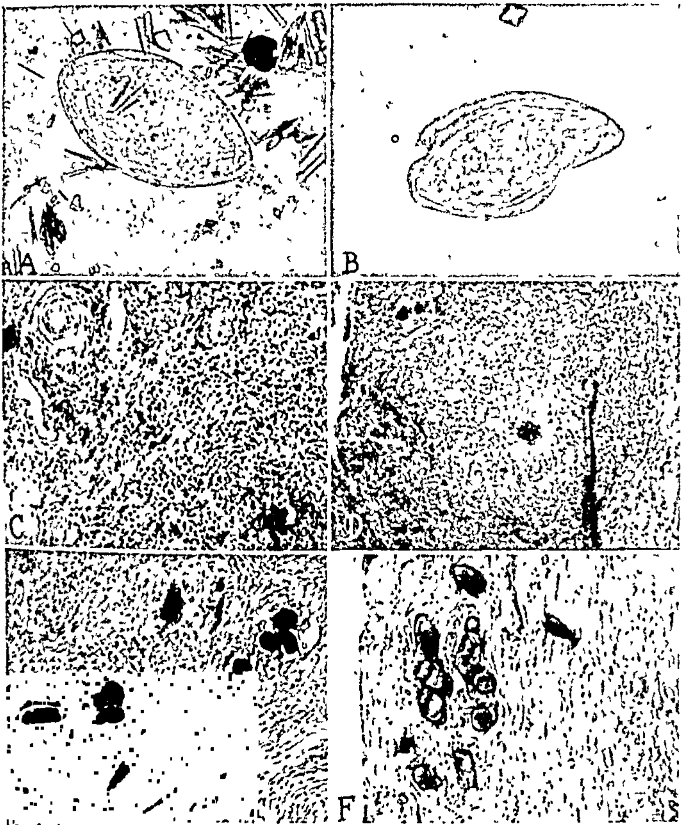

FIG 1. *A*, ovum of S. haematobium lying amidst calcium oxalate crystals. Terminal spine well shown *B*, miracidium appears breaking through shell of ovum. *C*, first biopsy to show ova (September 9, 1952). Note acute reaction. Main infiltrating cells are eosinophils. Beginning vascular proliferation is seen. *D*, intense response with necrosis in center was ringed by band of proliferating connective tissue cells with sparse to moderate infiltrate similar to *C* and outer ring of intense cellular infiltration. *E*, October 29, 1952, subacute reaction with beginning calcification of ova. Distinct terminal spine is seen at upper center. *F*, final biopsy November 17, 1952 Mucosa has been desquamated. Lesion progressing to chronic stage.

On August 29, 1952, cystosopy revealed bladder mucosa that appeared to be inflamed in spotty areas. These were composed of a small yellow center surrounded by a pearly gray border with a circumferential inflammatory reaction. The lesions were submucosal and measured 1–2 mm. in diameter.

Schistosomiasis was suspected and a biopsy was taken of one area. Although the left ureteral orifice was edematous, clear urine was seen flowing freely from both. The pathologic report from the first biopsy showed no schistosome ova.

On September 9, 1952, cystoscopy again disclosed infected mucosa with multiple yellow follicles in the posterior and lateral aspects and the base of the bladder. A biopsy confirmed the diagnosis of schistosomiasis. Subsequent examination on October 29, 1952 revealed that the reaction had not completely subsided. The biopsy on this occasion showed Schistosoma present in the bladder mucosa. On November 17, cystoscopy showed several areas of reaction still present and several small elevated lesions remaining. Biopsy again showed ova.

When the diagnosis of schistosomiasis of the bladder was made, the patient was placed on a course of Fuadin. This consisted of an initial daily intramuscular injection of 1.5 cc, 3.5 cc and 5 cc, followed by 5 cc every other day for 16 doses. A rest period of 2 weeks ensued. Even though improvement was noted, bilateral flank pain persisted. Examinations for ova during the rest period were negative. Because of the persistence of symptoms, Hetrazan* therapy was given for two weeks. The patient became asymptomatic and was discharged fit for duty to rejoin his ship. Adequate follow-up for five to ten years was advised.

Pathology: The bladder biopsy of August 29 showed mild chronic cystitis. There was a slight eosinophil infiltration.

The subsequent biopsy of September 9 revealed the ova of S. haematobium. The ova appeared with distinct terminal spines when the plane of section was proper to include this feature. The shell had been folded and retracted by fixation. The internal structure was composed of small basophilic nuclei nestled in basophilic granular amorphous material. In many instances this had also been differentially shrunken by fixation. Occasionally, medium to large cells with a vesicular nucleus and a pale eosinophilic, slightly granular cytoplasm with indistinct cytoplasmic boundaries were seen to lie immediately inside the shell. The presence of these ova had provoked three histologic pictures in the immediately surrounding tissues: 1) A group of ova lay in proliferating connective tissue with a sparse to moderate eosinophil infiltration. This was admixed with mononuclear cells and sparse numbers of neutrophils. The infiltration was quite intense immediately surrounding the ova and then became moderate for a small distance. An intense ring of infiltrate was seen at the periphery of the reaction (fig. 1, *C*). 2) An intense response with necrosis in the center was ringed by a band of proliferating connective tissue cells with a sparse to moderate infiltrate similar to the foregoing and an outer ring of intense cellular infiltration (fig. 1, *D*). Biopsy (September 9, 1952), necrotic tuberculoid type of reaction. 3) This type was much older. The ova were surrounded by giant cells of the foreign body type and lay in little masses in dense fibrous tissue. Cellular infiltration was extremely sparse and limited to a few monocytes and lymphocytes. Occasionally, this reaction presented a center of brightly eosinophilic, smudged material. All of these reactive foci lay in the submucosa which was edematous and thickened. There was a scant infiltration of eosinophils, monocytes and lymphocytes. An associated vascular reaction in the small vessels was manifested by slight to moderate intimal hyperplasia. The adventitia was also active, one vessel presenting an adventitial cell in mitosis. The mucosa presented some infiltration with eosinophils.

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* Lederle Laboratories Division, American Cyanamide Co., Diethyl Carbamazine 50 mg tablets. Hetrazan was used empirically. Its efficiency cannot be determined since improvement was noted during Fuadin therapy.

Resolution of the lesion had begun in the biopsy of October 29 and the intensity of the reaction had quieted markedly (fig. 1, *E*). The ova were calcifying. Some of the ova were completely calcified while others were in early stages with remnants of internal structure being seen. Foreign body giant cells were plentiful in juxtaposition to the ova. The fibroblastic proliferation was now replaced by more mature collagenous tissue. This had served to compress the ova-containing foci. Only scattered eosinophils were noted. The infiltrate, though sparse, was composed of lymphocytes and monocytes. The vascular reaction was subsiding. There remained some slight medial thickening and an occasional plump endothelial cell.

The healed fibrotic stage (fig. 1, *F*) was seen in the last biopsy. At this stage the ova appeared to be completely calcified. There was dense fibrosis of the submucosa surrounding the masses of calcified ova. A similar reaction was present in the areas of muscular involvement. Only a few scattered cells were noted; these were predominantly lymphocytes and monocytes. Eosinophils were a rarity. One section showed small nests of transitional epithelium beneath the surface as though chronic cystitis were developing.

DISCUSSION

The patient was referred to this hospital with a diagnosis of urinary calculus. The first inkling of his actual disease came from cystoscopy. The cystoscopic appearance of this lesion has been termed characteristic (Maker quoted Riba, Campbell, and Cummings). Gelfand emphasizes that a normal appearance of a bladder on cystoscopy does not rule out schistosomiasis and biopsy should be done. As the therapy progressed, the eosinophil count decreased. With the known vagaries of eosinophil counting, the relative fluctuations are not considered of importance. Although the eosinophil count is usually elevated, some cases do not show this feature (Goldey; Miller). This patient entered with bilateral flank pain.Excretory urograms showed an S-shaped dilatation in the lower left ureter. Edema of the left ureteral orifice was present on cystoscopy. Gelfand considers these findings significant in patients known to have schistosomiasis. Perhaps this patient had ureteritis concomitant with cystitis, although retrograde studies were not done to confirm this.

Because of the long life of the parasite, it is difficult to state where the infection of this seaman, of Egyptian nativity and Australian residence, occurred. The patient definitely stated that he had symptoms for only 5 months with one bout of hematuria during that time. He denied having hematuria at any previous time.

The finding of the characteristic ova or miracidia in the urine is diagnostic. However, Sayegh points out that 653 people suffering form S. haematobium infection were seen at the American Hospital in Tanta, Egypt in a two year period, yet parasites were not demonstrated in their urine. In our case, no ova or miracidia were seen before therapy was begun and then only on four successive days. For this reason cystoscopy and biopsy are probably the most efficient and quickest methods for making the diagnosis. In fact, Gelfand and Sayegh recommend that the biopsy material be crushed between two slides and examined under subdued light. More than one examination may be necessary to establish the diagnosis.

There is some indication in the second biopsy that more than one shower of ova had become implanted in the bladder as lesions of different ages were seen. This is characteristic of the infection as long as the adult parasites are alive. The biopsies themselves show the classic picture of the disease as given in the major texts in this field (Belding; Craig and Faust; Faust, 1939; Mackie, et al; Strong). However, none of the authors gave a time relationship between the stages, either with or without treatment. The resolution of the acute lesion to the chronic fibrotic type of reaction is presented. These are oriented in point of time with the Fuadin therapy. It is interesting to note that the gradual disappearance of eosinophils from the blood was coupled with their disappearance from the tissue. The vascular reaction has been thoroughly studied and Belding, quoting Koppish, mentions that the penetration of the ova into the tissues is accomplished, in part, by pressure and an endothelial and subendothelial reaction in the vessels. The reaction of the host tissue to the ova is said to be due, initially, to lytic secretions from the miracidia within the egg shell (Belding; Faust, 1948). Diffusion explains the circular configuration of the lesion in the beginning (Faust, 1948). The subsequent picture is that of a foreign body reaction. Calcification is the usual fate of an ovum. Dense fibrosis and contracture wall off the offending foreign matter. These lead to dysfunction of the organ in which they are taking place. In this regard, an article by Sayegh is most interesting.

When the diagnosis is made, treatment may be carried out with tartar emetic or stibophen (Fuadin). Therapeutic schedules are carried in the major texts (Belding; Craig and Faust; Faust, 1939; Mackie, et al; Strong) on this subject. The success of therapy may be judged, either by finding viable or nonviable ova in the urine or by biopsy of the bladder showing calcification of the ova and resolution of the acute reaction by fibrosis and contracture. Faust (1939) and Cummings comment that the relapse rate with Fuadin and tartar emetic is high and multiple courses may be necessary. Cummings maintains that a five to ten year follow-up is necessary from the standpoint of the infection. The residua from infection may not make themselves known for many months or years, especially if the infection is light (Miller).

The existence of potential reservoirs of this disease in our armed forces, merchant mariners, foreign seamen and travelers for business and pleasure may well present this lesion and its late complications to any of us for diagnosis and treatment.

SUMMARY

A case of Schistosoma haematobium of the bladder and probably left ureter is presented.

This is probably the first authentic case reported from the State of Washington.

Resolution of the lesion under Fuadin therapy as revealed by serial cystoscopic biopsies is discussed.

The useful diagnostic procedures are outlined.

The necessity of long term follow-up is indicated.

The ever-present problem of schistosomiasis presenting in the United States and Canada is noted.

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TUMORS OF THE BLADDER: SURVEY OF 180 PATIENTS

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Many urologists throughout the country are advocating radical surgery for the treatment of bladder tumors, regardless of the extent of the tumor or the pathological diagnosis. The reasoning behind a trend to early total cystectomy is based on two factors: 1) that the clinician cannot ascertain by clinical judgment whether or not a given bladder tumor, regardless of its size, configuration or location, will at some later date invade and kill the patient, and 2) that the pathological diagnosis is not reliable in determining the tumor's future growth and behavior.

The reason for this report is to show by careful investigation and long-term patient followup of tumors, which an experienced urologist diagnoses as clinically noninvasive, that very satisfactory results are obtained on a conservative surgical management. Total cystectomy and ureteral transplantation must be regarded as a very radical, and, in most instances, a debilitating procedure, and one which we believe should be reserved for patients with bladder tumors that are clinically and pathologically invasive.

METHOD

In this study, which includes the investigation of all applicable bladder tumor patients at Wesley Memorial Hospital from 1942 to 1952, the initial admission chart was carefully scrutinized for all pertinent information, and each additional admission chart checked for further helpful data. Next, the office records of these patients were thoroughly investigated to check the patient's status as to recurrences, treatment and general state of health for the followup. Finally, letters were sent to all patients who had not been seen recently to enable us to follow through with as complete a survival record as possible.

Herein we present a summary of the data extracted, with emphasis on survival.

GENERAL DATA

Of the two hundred or so case records studied, 180 patients with bladder neoplasm were acceptable for this investigation. On a few patients, sufficient information was lacking for proper inclusion. Sixty-five per cent of the patients were males and 35 per cent females (table 1). The disease developed in the majority between 60 and 70 years of age, about one-fourth were between 50 and 60, with lessening percentages from those ages down to small numbers in the third and ninth decades. The age range table illustrates this spread in percentage form.

As would be expected, most of the patients (87 per cent) had gross or microscopic hematuria, which most frequently first brought them to the urologist. Over half of the cases (55 per cent) had symptoms of bladder irritability such as frequency and/or nocturia. Nearly 40 per cent had some degree of pain or burning

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* Assisted by William Price, M.D.

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TABLE 1

Number of cases—180	Males—117 (65%)	Females—63 (35%)

Age Range

20–30	30–40	40–50	50–60	60–70	70–80	80–90
1.3%	5.0%	8.3%	25.5%	42 7%	14.4%	2.8%

Complaints:				
	Hematuria	87%	Frequency & nocturia	55.5%
	Dysuria	37.7%	Suprapubic pain	8.3%
	Flank pain	5.0%	Pyuria	1.0%

TABLE 2

Duration of symptoms when first seen:

0–3 mo	3–6 mo.	> 6 mo–1 yr.	1–2 yrs.	2–3 yrs	3–4 yrs	4–5 yrs	Over 5 yrs
43.0%	9.4%	20.0%	6.0%	6.0%	2.0%	2 0%	6 0%

Unknown—5 6%

G.U tract disease secondary to bladder tumor:		
	Hydronephrosis	22%
	Pyelonephritis	5%
	Fistulas	1%

Associated benign prostatic hyperplasia—33% of males

on urination. A much smaller number had suprapubic or flank pain, and still fewer suffered from pyuria.

We believe that an important factor in controlling bladder tumors is the promptness with which the patient seeks initial diagnosis and treatment and the subsequent attention he gives to his bladder health through frequent cystoscopic examination with fulguration when necessary (table 2). When first seen, 43 per cent, or nearly half of the patients, had experienced the symptoms of bladder tumor less than three months. Within one year of onset of symptoms, 69 per cent of the patients were under treatment. This figure coincides closely with the percentage of well-controlled patients, and, though it may be co-incidental, there is more reason to believe that a significant correlation exists.

Table 2 also shows that 22 per cent of the cases suffered some degree of hydronephrosis secondary to the bladder tumor, 5 per cent had pyelonephritis (unilateral or bilateral) and 1 per cent had rectovesical fistula. As a sidelight we determined that 33 per cent of the males, regardless of consideration as to age, had some degree of benign prostatic hyperplasia. This is slightly higher than most statistics reveal for men over 60.

PATHOLOGY

For several reasons, the pathological data are incomplete, and, at the same time, somewhat redundant as regards pathological classification of the tumors. In the first place, the followup includes cases back to 1942, at which time pathological diagnoses were far from uniform and clear cut. Secondly, Wesley Memorial Hospital has had several pathologists during that period of time. The present

TABLE 3. *Pathological types of bladder tumors*

	NONINVASIVE	INVASIVE	TOTAL
Transitional cell carcinoma	39 (30 7%)	22 (52.4%)	61
Transitional cell papilloma with malignant change	19 (14.9%)	2 (4.8%)	21
Transitional cell papilloma	16 (12.6%)	—	16
"Benign" papilloma	8 (6.3%)	—	8
Bladder polyps (? papilloma)	3 (2 3%)	—	3
Papilloma with malignant change	6 (4.9%)	9 (21.4%)	15
Carcinoma simplex	3 (2.3%)	3 (7.2%)	6
Adenocarcinoma	1 (1.0%)	—	1
Mucinous adenocarcinoma	2 (1.5%)	—	2
Undifferented carcinoma	3 (2.3%)	2 (4.7%)	5
Squamous cell			7

staff is very adept and accurate in their diagnoses, so that the tissues for the last seven years have been more accurately diagnosed. Finally, not in every case was a specimen sent for biopsy, though the clinical diagnosis was definite.

Table 3 illustrates the pathological types. Of 115 clinically diagnosed, noninvasive tumors, 105 were biopsied. Thirty per cent were diagnosed transitional cell carcinoma, 15 per cent transitional cell papilloma with malignant change, and 20 per cent fell into the benign papilloma group, including the transitional cell papillomas and bladder polyps. In the clinically invasive group of 41 cases, 38 were biopsied, and over 50 per cent proved to be transitional cell carcinoma and 21 per cent were papillomas with malignant change. Finally, there were seven cases of squamous cell carcinoma in our series. Of some interest, it is surprising that our three cases of adenocarcinoma were clinically noninvasive, and all are alive and well at this writing.

SURVIVAL TOTALS

Of the 180 cases included in our study, 18 were not included in the survival totals because of inadequate followup data. To all patients who had not been seen recently, either in the hospital or office, letters of inquiry were written. Eighteen persons failed to answer and are not, therefore, included.

Table 4 is a summary of the status of each patient at this writing without regard to length of time followed. Subsequent tables will discuss the length of survival. In table 4 we have divided the cases into three groups: 1) clinically noninvasive tumors as per the initial diagnostic impression; 2) clinically invasive tumors when first seen; 3) squamous cell tumors. Furthermore, because there is debate as to the validity of open suprapubic coagulation of bladder tumor, we divided the cases into two additional groups: –1) those treated by transurethral coagulation only, and 2) those controlled by suprapubic coagulation with or without subsequent transurethral coagulation. The criterion for the type of surgical approach was based on the size, location and accessibility of the tumor with consideration as to degree of invasiveness.

Table 4 shows that of 115 noninvasive tumors, 59 were treated by transurethral coagulation alone (from one to many times, depending upon the number

TABLE 4 *Survival totals*

	NO. OF CASES	ALIVE & WELL	DEATHS	SEVERE RECURRENCE	SURVIVED STATUS?
Noninvasive (T.U.R.)	59	74.0%	20.3%	—	—
Noninvasive (open surg.)	56	60.7%	19.8%	5.3%	11.2%
Totals	115	68.8%	20%/6.9%	2.6%	8.6%
Invasive (T.U.R.)	11	—	81.8%	18.2%	—
Invasive (open surg.)	30	13.3%	70.0%	16.7%	—
Totals	41	9.7%	73.1%/48.3%	17.2%	—
Squamous cell (T.U.R.)	1	—	100.0%	—	—
Squamous cell (open surg.)	5	20.0%	60.0%	—	20.0%
Totals	6	16.7%	66.6%/66.6%	—	16.7%

Survivals—18 (letters written, not answered)

of recurrences). As of this writing, 74 per cent are alive and well and 20 per cent are dead. Of the 56 cases treated by suprapubic cystotomy and coagulation, 61 per cent are alive and well, 20 per cent are dead, 11 per cent are alive but with questionable tumor status and 5 per cent are still having severe recurrences. In summary, of the noninvasive tumors, nearly 70 per cent are alive and well and only 20 per cent are dead, but, of still greater importance, as per the second figure in the totals under the deaths column, only 6.9 per cent actually died of bladder tumor.

Of interest is the fact that the patients with noninvasive tumor show approximately a 70 per cent alive and well survival regardless of the surgical approach. It seems, therefore, that suprapubic cystotomy does not promote the spread of tumor and enables a more thorough eradication of the larger, less accessible neoplasms.

Of the 41 cases of invasive bladder tumor, only 11 were treated solely by transurethral coagulation. Of these, 82 per cent are dead and 18 per cent are having severe recurrences and 13 per cent are alive and well. In summary, we see a discouraging picture for those patients diagnosed initially as having invasive bladder tumors. Seventy three per cent are dead, nearly 50 per cent of the total having died from their tumor. Seventeen per cent are alive with severe recurrences and only a scant 10 per cent are alive and well.

Squamous cell tumors, of which we report 6 cases, are equally discouraging. Only one was treated by resectoscopic coagulation, and he died of his tumor. Of 5, managed by open surgery, 3 are dead, one is alive and of questionable status, and one is well. The totals show that two-thirds died of their disease and only one patient survived with good health.

SURVIVAL PERIODS

Of major interest to us in summarizing these case histories is a record of the overall survival period, that is, the period of time from the date of the patient's

TABLE 5. *Survival period chart: Noninvasive tumors*

TOTALS		PERIOD OF OBSERVATION AFTER ONSET						
		0–6 mo.	6 mo.–1 yr.	1–2 yrs.	2–3 yrs.	3–4 yrs.	4–5 yrs.	Over 5 yrs.
Alive & well	79	100%	—	50%	66.7%	78.6%	70%	77%
Deaths	23/8	—	100%/66.7%	33.3%/16.7	16.7%/0	0/0	30%/15%	12.5%/0
Severe recurrences	3	—	—	5.5%	8.6%	7.1%	—	—
Alive status?	10	—	—	11.0%	8.6%	143.%	—	10.5%
Total	115	1	3	18	12	14	19	48

KNOWN SURVIVAL: 115 PATIENTS. *ALIVE & WELL:* 68.7%. *DEATHS:* 20%. *OF CANCER:* 7.0%. *SEVERE RECURRENCES:* 2.6%. ALIVE-STATUS?: 8.7%.

TABLE 6. *Survival period chart: Invasive tumors*

TOTALS		PERIOD OF OBSERVATION AFTER ONSET						
		0–6 mo.	6 mo.–1 yr.	1–2 yrs.	2–3 yrs.	3–4 yrs.	4–5 yrs.	Over 5 yrs.
Alive & well	4	—	—	—	—	25%	—	30%
Deaths	30/20	100%/100%	77.7%/22.2%	90%/63.6%	80%/60%	50%/50%	—	50%/40%
Severe recur	7	—	22.3%	9.1%	20%	25%	—	20%
Alive-status?	0	—	—	—	—	—	—	—
Totals:	41	2	9	11	5	4	0	10

KNOWN SURVIVALS: 41 PATIENTS. *ALIVE & WELL:* 9.7%. *DEATHS:* 73.3% *OF CANCER:* 48.8%. *SEVERE RECURRENCES:* 17.0%.

first bladder symptoms to the present time, with determination of their current health status.

As stated previously, all but 18 patients have been brought up to date in this study. They, or their relatives, failed to answer questionnaires as to their status. Tables 5 and 6 are constructed to illustrate the number of patients followed for each listed time interval and the percentages alive and well, dead, alive with severe recurrences, or alive and of questionable status in each time period. Further, of those dead, in each column the percentage who definitely died of their bladder tumor is listed to the right of the total per cent dead.

Table 5 includes the 115 cases of clinically noninvasive bladder tumors. Note that in the horizontal column marked total 48 cases lived over 5 years, 19 lived 4 to 5 years, 12 lived 3 to 4 years, 18 for 2 to 3 years, 3 survived only 6 months to 1 year, and 1 patient was followed from zero to 6 months.

Of the 48 patients who lived over 5 years, many of whom have been followed eight to ten years, 77 per cent are alive and well. Only 12.5 per cent are dead and the most remarkable observation is that *none* died of his bladder tumor. A scant 10 per cent are of unknown status, though alive. Of the nineteen who have been followed four to five years, 70 per cent are alive and well, 30 per cent are dead and 50 per cent of them died of their tumor, or 3 patients. Fourteen patients were observed three to four years and nearly 80 per cent of them are alive and well. Not one of this group of patients has died. A small fraction (7 per cent) are having severe recurrences and 14 per cent are of questionable status. Over 65 per cent of the 18 patients observed two to three years are alive and well, 33 per cent are dead—50 per cent of their bladder disease. Therefore, of the patients with initially noninvasive tumors followed more than two years, about 75 per cent are alive and well.

The 18 patients in this group seen from one to two years show only 50 per cent alive and well, 33 per cent are dead with half of these dead of tumor, and 11 per cent of questionable status. Five per cent are having severe recurrences.

Apparently, of the 3 patients followed 6 months to 1 year, two had pathologically invasive tumor, though clinically the tumors appeared noninvasive. These 2 patients died shortly after their first surgical procedure.

One patient who was recently seen at the time of this writing is alive and well.

The summary shown at the bottom of table 5 strikingly points out that only 7 per cent of 115 patients who lived from 6 months to well over 5 years, died of their tumor. Therefore, 93 per cent were effectively controlled and 68 per cent alive and well, as managed by either or both suprapubic and transurethral coagulation.

Table 6 includes an interval breakdown of the 41 patients diagnosed initially as having invasive bladder tumors. Ten lived over 5 years, and, of these, four died of their tumor, two are having severe recurrences and three are alive and well. Of four who were followed 3 to 4 years, two died of their tumor, one has severe recurrences and one is alive and well. Of the 27 patients observed up to 3 years, none are in good health. In the two to three year group, four out of five died and one is having severe recurrences. Of 11 who were followed one to two years, the largest single group in the invasive tumor category, 90 per cent ar dead, 64 per cent of their tumor. Of 9 patients in the six months to one yea group, 78 per cent are dead, but only 22 per cent definitely of cancer. Twenty-tw per cent have severe recurrences. Finally, both patients followed less than months died of tumor.

Table 6 is a discouraging reflection of the results in treating invasive tumor b coagulation. Of 41 patients, only 10 per cent are alive and well; whereas, 7 per cent are dead, 50 per cent of their cancer.

CONCLUSIONS

On initial cystoscopic or suprapubic examination of the bladder, the surgeo must determine to the best of his ability the degree of invasiveness of the tumor His judgment should be re-inforced whenever possible by biopsy and pathologica report of degree of invasiveness.

For those tumors placed in the noninvasive class, suprapubic resection an coagulation or transurethral coagulation alone, depending on size, location an type of tumor, provides adequate therapy with an excellent chance for a lon survival.

There is no evidence of increased morbidity or spread of the cancer cells by th suprapubic approach and the advantages are numerous.

Uniformly poor results occur with invasive bladder tumors by the applie methods of conservative surgery and with those cases, which on initial examination show a moderate to high degree of invasiveness, the advisability of radica cystectomy early in the course of the disease, with diversion of the urinar stream to bowel or skin, should be seriously considered. It is possible that subsequent work with radioactive colloids may provide an additional means o treating invasive tumors but, as yet, this is in the experimental stage.

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LEIOMYOSARCOMA OF THE URINARY BLADDER: REPORT OF A CASE

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In 1949 we had the opportunity of treating a patient who had a leiomyosarcoma of the urinary bladder. This is an infrequently encountered lesion, but even more unusual is a survival for longer than one year. Of the 25 cases reported to date, only two have been alive without recurrences 1 year following treatment. Hager and Hunt's patient was "alive and well" 4 years after operation, and Ley and Bell reported a case in which they speculated, "the prognosis to be good for complete cure in this instance", although no follow-up was presented. The subject of the following case report is alive, well, and without recurrences some 3 years and 3 months following surgical excision of the tumor.

CASE REPORT

P. P. K., Register Number 16-266, a 21 year old Negro, was admitted to the Thayer Veterans Administration Hospital on February 4, 1949 complaining of "bleeding when I pass my water."

Three weeks prior to hospitalization he suffered the insidious onset of dysuria, frequency, urgency, and bilateral costovertebral angle pain of a dull and constant nature. He was seen at that time by his family physician who prescribed sulfadiazine. The symptoms persisted despite this therapy, and one week later he began to urinate gross blood for the first time in his life. The bleeding occurred throughout the act of micturition and clots were passed painfully from time to time. He denied having fever, chills, weight loss, suprapubic pain, increased fatigue, or a urethral discharge during the present illness.

Pertinent past history revelations were that in 1947 he was successfully treated for gonococcal urethritis by penicillin, and that he had had recurrent episodes similar to the present illness since 1947, but never previously complicated by hematuria. Because of the unrelenting hematuria he sought hospitalization.

On admission to the hospital his blood pressure was 120/70, pulse 80, respirations 20, temperature 98.6F. He was a healthy appearing, young Negro in no distress. The mucous membranes of the oral cavity were unusually pale. The lungs were normal. The heart was normal except for a soft systolic murmur at the base. The abdomen was scaphoid, somewhat tense, but without tenderness. There were no palpable abdominal organs or masses. Mild tenderness was present in both costovertebral angles. The genitalia were normal. The prostate was boggy, somewhat tender, and moderately enlarged. There were no palpable rectal masses and no blood. The remainder of the physical examination was within normal limits. No urethral secretion was obtained by massage. Observation of the patient voiding confirmed the history of gross hematuria throughout the act.

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The results of the laboratory tests were as follows: hemoglobin 7.5 gm.; red blood count 3,500,000; white blood count 11,250; differential white count, normal; sickle cell preparation negative for sickling at 24 hours. Urinalysis: reaction, acid; specific gravity 1020; albumin 4 plus; sugar, negative. Microscopic: gross blood; no casts. Staphylococcus aureus was cultured from the urine. The phenolsulfonphthalein excretion was 45 per cent in 15 minutes; nonprotein nitrogen was 25.9 mg. per cent; sulfadiazine blood level, 0 mg. per cent; Kahn, negative. The chest x-ray was normal. An excretory urogram was normal. Cystogram revealed some slight flattening of the anterior aspect of the bladder. Cystoscopic examination was carried out on February 11, 1949, under local anesthesia. An elevated, irregular, ulcerated tumor, approximately 2 cm. in diameter was found to involve the anterior bladder wall. The tumor was biopsied, but on microscopic section neoplastic cells could not be found, rather only those inflammatory changes of cystitis. Subsequently on February 16, 1949, the cystoscopic examination was repeated under spinal anesthesia. The findings were unchanged, though some gross edema had developed in the interim about the site of the previous biopsy. What was thought to be a more adequate biopsy was taken at this time and the area fulgurated. Once more the microscopic sections contained only inflammatory changes and no evidence of tumor. Following cystoscopy, a bimanual examination under spinal anesthesia revealed a spherical mass calculated to be about the size of an English walnut, which was freely movable and thought to be within the wall of the bladder. The cystograms were repeated, and this time more clearly demonstrated the defect in the anterosuperior wall of the bladder (fig. 1). During this period of diagnostic procedures, the anemia was corrected by whole blood transfusions despite continuation of the bleeding, and the urine became sterile on penicillin therapy.

On March 7, 1949, under spinal anesthesia, a midline suprapubic approach was employed to explore the bladder. On gaining the prevesical space, an egg-sized, circumscribed mass was found to be presenting anteriorly from its incor-

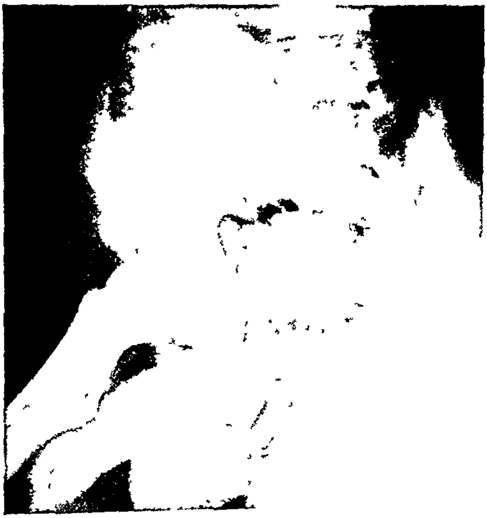

FIG. 1. Defect in anterior bladder wall as demonstrated by cystogram

poration within the anterior bladder wall. An attempt to dissect the peritoneal reflection off the tumor and bladder was fraught with the possibility of entering the tumor due to the firm adherence of the peritoneal reflection to the tumor, and was, therefore, abandoned. Consequently, the peritoneum was incised in such a manner that that portion of peritoneum attached to the tumor was undisturbed. The resultant peritoneal defect was closed transversely with a continuous catgut suture. The tumor with the attached islet of peritoneum was then excised from the bladder by dividing all layers of the bladder with the circumscribing incision. Frozen sections showed the tumor to be a sarcoma. It was felt that removal of more tissue about the periphery of the defect might improve the prognosis; therefore, a 2 cm. cuff of normal appearing bladder wall was excised circumferentially about the defect. The remaining bladder did appear quite small, but closure of the cystotomy wound about a Malecot catheter did not appreciably alter the trigonal structures. The abdominal wound was then closed in the usual manner, after placing a rubber tissue drain in the prevesical space.

Grossly the specimen consisted of a firm, ovoid tumor mass, 6 by 4 by 3.5 cm. in size, well contained within the surrounding fascia and fibrous tissue and on one surface covered by bladder mucosa. The cut section was composed of pale gray, fleshy tissue with rather large areas of yellowish necrosis (fig. 2).

Microscopically the tumor was fairly well circumscribed, but active invasion of the bladder muscle was evident in several sections (fig. 3). The tumor was composed of interlacing bundles of spindle cells with plump oval or elongated nuclei and rather abundant cytoplasm (fig. 4, *A*). The cells composing the tumor stained selectively for smooth muscle by Masson's trichrome method. The more peripheral areas were compactly cellular and occasional mitotic figures were seen (fig. 4, *B*). In the more central portions the cell bundles were edematous and large areas of necrosis were present. The blood supply of the tumor was by endothelial lined sinusoids, surrounded closely by neoplastic cells.

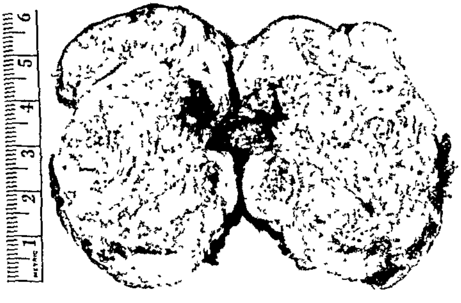

FIG. 2. Cut section of tumor at its greatest diameter. Section consists of whorls of fleshy gray tissue with large areas of yellowish necrosis.

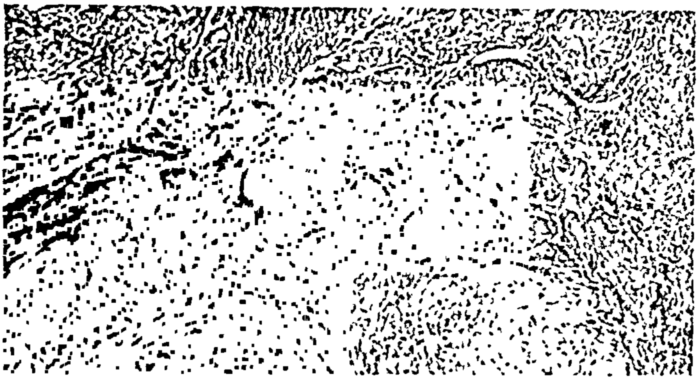

FIG. 3. Upper portion of section represents pre-existing bladder musculature with peninsula extending downward which is surrounded and invaded by tumor. Portion of tumor on right is edematous.

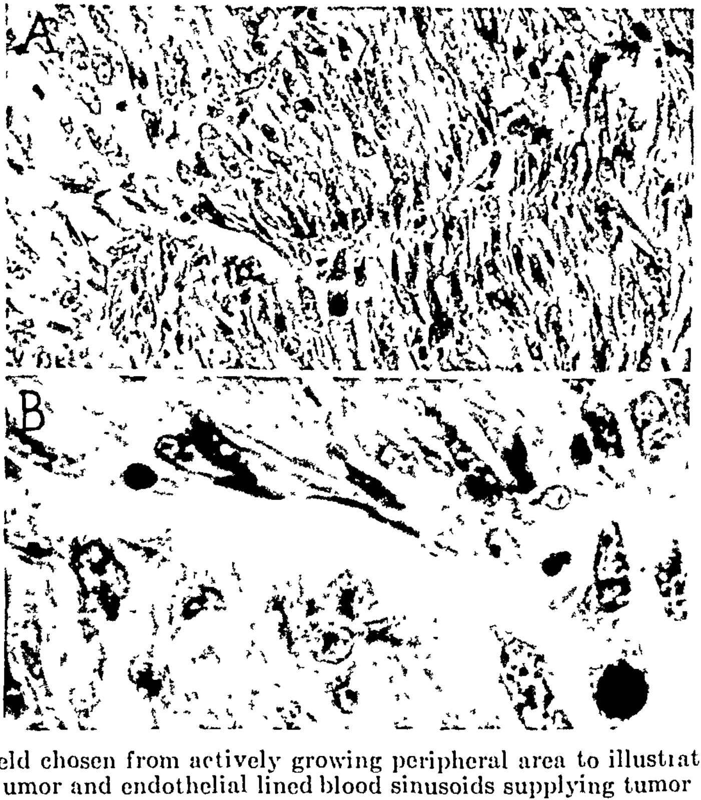

FIG. 4. *A*, field chosen from actively growing peripheral area to illustrate rather dense cellularity of tumor and endothelial lined blood sinusoids supplying tumor Mitotic figure is present in center of field. *B*, higher power of mitotic figure shown in *A*.

The postoperative course was uneventful except for the culture of B. cloacae from the urine. This infection subsided on sulfasuccidine treatment. The suprapubic wound had closed by the fourteenth postoperative day and he was voiding without difficulty. The bladder capacity one month postoperatively was 8 ounces, as determined by the maximum amount of urine the patient could retain without undue distress. When the patient returned for the first follow-up visit 4 months postoperatively, he was complaining of a urethral discharge and dysuria, but no more bleeding. A smear of the discharge disclosed gram negative intracellular diplococci. The gonococcal infection was cured by penicillin and sulfadiazine. Later, cystoscopy revealed no evidence of recurrence of the tumor and the bladder was considered normal.

Subsequently, this patient has been followed at six month intervals, with no evidence of recurrence of the tumor.*

DISCUSSION

Due primarily to the compilation of cases of leiomyosarcoma by Kretschmer and Doerhing, and Crane and Trembly, together with case reports by Lev and Bell, Mackles, et al., and Fister and Lund, some of the characteristics of this unusual tumor have come to light. The signs and symptoms do not deviate from those of the more common bladder neoplasms, hematuria being the cardinal sign. The tumor occurs in the male three times more frequently than in the female. It has been seen to arise from all parts of the bladder wall, but usually at some distance from the trigone, and none has been reported as being primary in the trigone. If one discounts the case of Mackles, et al., in which there was not only sarcoma but also a papillary carcinoma, there are only 2 cases in the series in which distant metastases were demonstrated.

Unfortunately, these tumors may grow outwardly and peripherally for a considerable time before invading the mucosa and causing hematuria, or they may produce hematuria at an earlier date, as in our case. Therefore, the time from the onset of hematuria to treatment is not a reliable criterion of the duration of growth of the tumor. Certainly, the sooner definitive treatment is instituted following the onset of symptoms the more favorable will be the prognosis.

The fact that this tumor rarely metastasizes should make it one of those most amenable to local radical excision and the overall results should be improved. Wide local removal is, therefore, the treatment of choice, whether it requires only a segmental cystectomy, a total cystectomy, or a radical pelvic evisceration. Today, with the newer operative techniques and supportive measures, we should be able to lengthen the survival time of patients with this type of malignancy, and possibly, and we say this with some trepidation, obtain a cure.

SUMMARY

A case of leiomyosarcoma of the urinary bladder is reported. The patient is alive, well, and without recurrence 3 years and 3 months following surgical excision.

Some of the characteristics of this rare bladder neoplasm are discussed, and it is speculated that the survival time should be improved with local radical surgical excision.

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* The patient moved to Camden, Ohio, in September 1951, and we are indebted to Dr. Dale T. Mullins and the Urology Staff of the Cleveland Veterans Administration Hospital for the more recent follow up examinations.

ADDITIONAL DATA

We have received a report from Dr. A. P. Rhamy of Crile V. A. Hospital, Cleveland, Ohio, dated March 25, 1954, stating that a cystoscopic examination on that date revealed no recurrence of the tumor.

H. S. S.

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MUCINOUS ADENOCARCINOMA IN A URACHAL CYST PRODUCING PSEUDOMYXOMA PERITONAEI

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Pseudomyxoma peritonaei was first reported by Wells[1] in 1865 when he described two cases of myxomatous degeneration of the peritoneum associated with mucinous cysts of the ovary. For over three decades this condition of "mucous ascites" was only seen in cases in which an ovarian lesion with mucoid elements was present In 1901, Frankel[2] reported a case in which a ruptured mucocele was found in the appendix of a man. Since then, pseudomyxoma peritonaei has been described as occurring secondary to mucinous adenocarcinoma of the gallbladder, of a caecal diverticulum or of a remnant of the omphalomesenteric duct [3] In the majority of cases, however, it is associated with a low grade pseudomucinous cystadenocarcinoma of the ovary, and in most of the remaining cases it is associated with a similar lesion of the appendix

Hayes and Segal[4] reviewed the literature on this subject in 1945 and established the fact that tumors arising in a urachal remnant are usually adenocarcinomas and that the majority of these are of the mucinous type Begg[5] has satisfactorily accounted for this from the histologic standpoint by demonstrating that the urachus represents a division of the original cloaca, and its cuboidal epithelium has retained the potential for producing mucin. Loeb,[6] Hurwitz, Jacobson and Ottenstein,[7] and other authors have reported cases in which a mucinous adenocarcinoma arose in the urachus and invaded the bladder In a cursory review of the literature, we were unable to find a report of a case in which pseudomyxoma peritonaei was associated with a urachal cyst The following case represents such an occurrence

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[*] Now practicing in Phoenix, Arizona

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REPORT OF CASE

A salesman, aged 65 years, came to the Mayo Clinic on July 31, 1951, because of a dull, continuous ache which had been present in the left lower quadrant of the abdomen for 6 weeks and had increased gradually in severity. The dull ache had been accentuated slightly by constipation, coughing or long automobile rides. Defecation or assuming the supine position had afforded some relief. The ache was not associated with nausea, diarrhea or other gastro-intestinal symptoms. The patient had lost 10 pounds (4.5 kg.) in the preceding year.

Nocturia had been present for 4 or 5 years, and the patient had had to micturate once or twice each night. Dribbling of urine occasionally had occurred after micturition. The patient had had an attack of appendicitis in January 1950, and appendectomy had been performed at that time.

Physical examination revealed moderate tenderness to the left of the umbilicus and prostatic hypertrophy, grade 2 (on the basis of 1 to 4). The enlarged prostate gland felt benign. Rectal examination disclosed small, external and internal hemorrhoids. The results of laboratory tests were normal. Roentgenologic examination of the thorax, colon and lumbar segment of the vertebral column did not reveal any abnormality. Excretory urography did not reveal any apparent abnormality of the urinary tract, but it did disclose a shadow caused by calcification and situated just above the vesical area (fig. 1). This was considered suggestive of calcification within an intra-abdominal cyst.

Because the symptoms subsided almost entirely, the patient was permitted to return to his home on August 8, 1951. An anticonstipation diet was prescribed, and the patient was advised to return to the clinic if his symptoms persisted.

The patient returned to the clinic on May 8, 1952. The dull, aching pain had shifted to the suprapubic area, and had increased in severity. It had been associated with a bearing down sensation. The signs and symptoms of urinary obstruction had become more pronounced, and the patient had noted an interruption of his urinary stream.

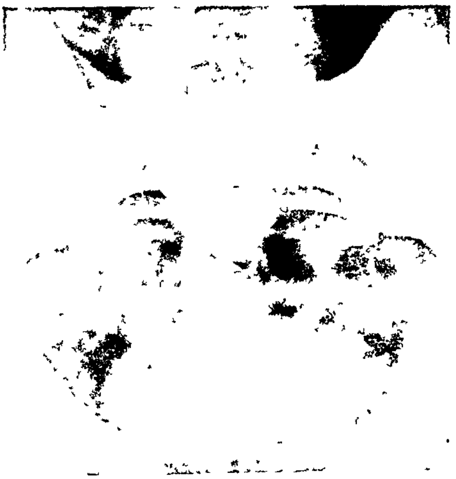

FIG. 1. Crescentic shadow of calcification above vesical area

The results of physical examination were the same as they had been at the time of the previous examination. The results of laboratory tests and roentgenologic examination were normal. The bladder contained 10 cc residual urine Cystoscopy disclosed enlargement of both lateral lobes of the prostate gland which appeared to be causing urinary obstruction.

On May 5, 1952, 32 gm. of prostatic tissue was removed by means of transurethral resection. Pathologic examination of the excised tissue revealed adenofibromatous hyperplasia. The suprapubic pain disappeared after the operation When the patient was dismissed on June 11, 1952, he mentioned that the dull ache in the left lower quadrant of the abdomen had returned This ache apparently had been overshadowed by the suprapubic discomfort prior to the operation.

The patient again returned to the clinic on December 11, 1952. The pain in the left lower quadrant of the abdomen had increased in severity, and the patient had been able to obtain relief only by lying in the prone position. He had lost 5 pounds (2 3 kg.) since his last visit to the clinic.

Physical examination revealed that the tenderness still persisted in the left lower quadrant of the abdomen. Palpation did not disclose any abdominal mass Laboratory tests did not reveal any abnormality, but roentgenologic examination of the stomach disclosed a small diaphragmatic hernia. Roentgenographic examination of the abdomen did not reveal any change in the crescentic shadow which was noted at the time of the patient's first visit to the clinic.

An exploratory laparotomy was performed on December 15, 1952. Mucinous material was present throughout the peritoneal cavity. Microscopic examination of this material disclosed a mucinous adenocarcinoma, grade 1. A calcified mass, which measured 4 by 3 cm., was situated on the anterior abdominal wall near the dome of the bladder The mass, which apparently was a cyst of the urachus, was removed (fig 2). The pathologist reported that the surgical specimen con-

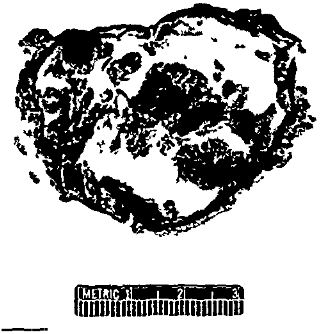

FIG 2 Adenocarcinoma of urachal cyst Wall of cyst is thickened, and cyst contains mucus

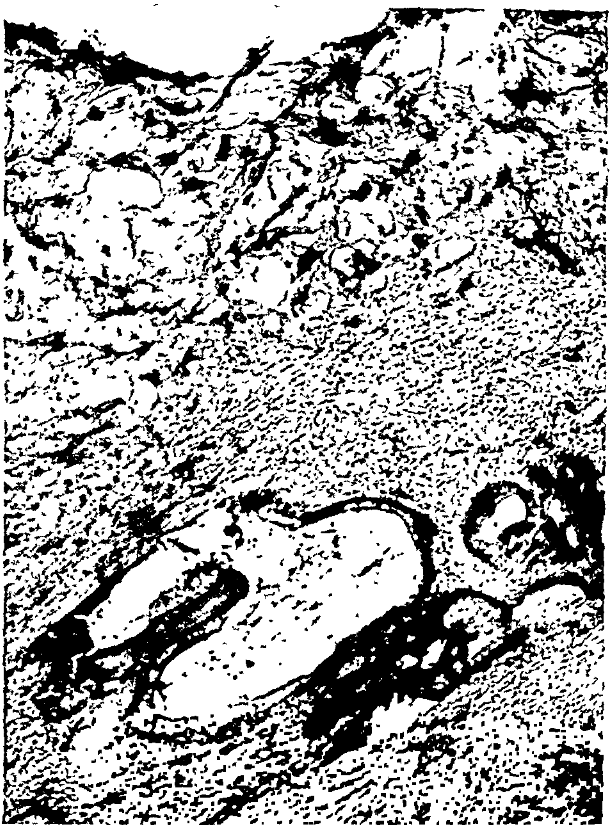

FIG. 3. Mucinous adenocarcinoma of urachal cyst (hematoxylin and eosin stain; × 42).

sisted of a multilocular, encapsulated, calcified mass, which was 4 cm. in diameter and contained a mucinous adenocarcinoma, grade 1 (fig. 3).

In order to exclude the appendix which had been removed elsewhere as the primary source of the mucinous adenocarcinoma, multiple sections of this organ were examined through the courtesy of Dr. R. E. Weland (Cedar Rapids, Iowa). There was no evidence of a mucocele or neoplasm being present.

His postoperative course was uneventful and he was dismissed from the hospital on December 27, 1952, and returned home on December 30, 1952. Arrangements were made for the patient to receive roentgen therapy to the entire abdomen. He was to return to the clinic in three months, at which time the advisability of intraperitoneal administration of radioactive colloidal gold was to be considered.

COMMENT

The surgical finding of mucus scattered throughout the peritoneal cavity and the histologic finding of slowly growing adenocarcinoma producing this mucus are the features which are necessary for a diagnosis of pseudomyxoma peritonaei. Such a combination of circumstances was found in the case which we have reported. It is not sufficient merely to have mucus in the peritoneal cavity because it is possible for a benign cyst which contains mucus to rupture and spill the mucoid material throughout the peritoneal cavity. This will be absorbed unless there is an associated implantation of glandular tissue from carcinoma cells which continues to produce more mucus. In most cases of pseudomyxoma peritonaei the primary source of the mucoid material has been a mucinous cystadenocarcinoma of the ovary. Less commonly, a malignant mucocele of the appendix has been the source of the material. An occasional case has been reported in which a retroperitoneal cystadenocarcinoma beginning in a cyst has been the primary source.

SUMMARY

This report is based on a case in which a mucinous adenocarcinoma developed in a calcified urachal cyst and extended intraperitoneally to produce pseudomyxoma peritonaei. The necessity of ruling out a urachal cyst as the site of origin of pseudomyxoma peritonaei is worthy of mention.

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PROLAPSE OF THE URETHRA IN YOUNG GIRLS

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Moffett and Banks[1] recently reported 4 cases of prolapse of the urethra in Negro girls between the ages of three and seven. They stressed the relative rarity of this condition in young girls as other authors[2, 3, 4] have done, and suggested a simple form of treatment. Within a period of 8 months we have seen and treated four young girls for a protrusion of the urethra through the meatus. The fifth case included in this series was a private patient of a member of our staff. All the patients were young, well nourished and well developed Negro girls. The youngest was 3 years of age and the oldest was eight. The purpose of this publication is to report these 5 cases of prolapse of the urethra in young girls and to re-affirm the effectiveness of simple complete circular amputation with a cautery loop in the treatment of this disease.

REPORT OF CASES

Case 1. D. L., a 3 year old Negro girl, was brought into the hospital by her mother because she noticed that the child was "bleeding from her privates." The mother reported that during the previous 12 months the child had many upper respiratory infections which were usually associated with frequent bouts of severe coughing. The mother particularly noted that it was during a coughing spell that she saw blood "running" from the genitalia for the first time. There were no associated urinary symptoms. Physical examination revealed an injected pharynx with a mucopurulent discharge from both nostrils. Examination of the vaginal introitus demonstrated a dark red edematous circular prolapse of the urethral mucosa which measured approximately 1.5 cm. in diameter and protruded about 0.5 cm. The mass was tender and bled easily when touched. After the upper respiratory infection had subsided, laboratory studies including a catheterized urine specimen, complete blood counts, Kahn test, excretory urogram and observation cystoscopy were completed and were found to be normal. The urethral lesion was first treated with hot sitz baths, and on the fifth day the entire prolapse was excised without any difficulty by the cautery loop. No approximating sutures were used. Bleeding was insignificant. The patient was allowed out of bed the evening of surgery and was discharged on the fourth postoperative day. She was last seen two months after the operation. Urinary symptoms and evidence of stricture formation were absent.

Case 2. B. J. G., a 4 year old Negro girl, was admitted to the hospital because

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Accepted for publication July 17, 1953.

[1] Moffett, J. S., and Banks, R. Jr.: Prolapse of the urethra in young girls. J.A.M.A., **146:** 1288, 1951.

[2] Zeigerman, J. H. and Kimbrough, R. A.: Circular prolapse of the urethra. Am. J. Obst. and Gynec., **56:** 950, 1948.

[3] Klaman, E. H., Mansfield, W. K. and Schoenbucher, A. K.: Circular prolapse of female urethra. South. Med. J., **42:** 929, 1949.

[4] Berry, N. E. and Greene, H.: Prolapse of the female urethra. J. Urol., **39:** 92, 1938.

of bleeding from the vagina. Her mother related that the child had had one episode of similar bleeding four months previously. This subsided spontaneously without any treatment. At no time were there any urinary symptoms. Examination revealed an edematous, inflamed prolapsed urethral meatus measuring approximately 1 cm. in diameter. At the most dependent portion of the prolapse was a small ulcerated area. A catheterized urine specimen, Kahn test, observation cystoscopy and excretory urogram were normal. The patient was treated with hot sitz baths for 5 days and then the prolapsed urethral mucosa was removed flush with its base with the cautery loop. Bleeding was minimal. The patient made an uneventful recovery and was discharged on the fifth postoperative day. She was last examined 3 months following the operation and had no stricture of the urethral meatus.

Case 3. J. A. S., an 8 year old Negro girl, was admitted to the hospital complaining chiefly of burning on urination of 5 days' duration. Her mother also stated that the child had a "swelling in the vagina" which she first noticed 3 years earlier following a criminal attack. The swelling apparently had not increased in size during this interval. There were no other complaints. Examination revealed a noninflamed prolapse of the urethra. The mass measured 1 cm. in diameter and protruded approximately 0.4 cm. A catheterized urine specimen, blood counts, Kahn test and excretory urogram were all normal. Observation cystoscopy demonstrated mild trigonitis and urethritis. The lesion was first treated with hot sitz baths and on the third day, the prolapsed mucosal cuff was removed with the cautery loop. A slight amount of bleeding occurred on the day of the operation but this cleared spontaneously at the end of the 12 hours and catheterization was not necessary. The patient was discharged on the fourth postoperative day. She was examined 2 months after the operation and had no urinary difficulties or any evidence of stricture formation. A No. 18 infant sound was easily passed into the bladder. Figure 1 shows the preoperative and postoperative photographs.

Case 4. B. B., a 3 year old Negro girl, was admitted to the hospital because her mother had noticed during the previous 2 days "spots of blood" on her under-

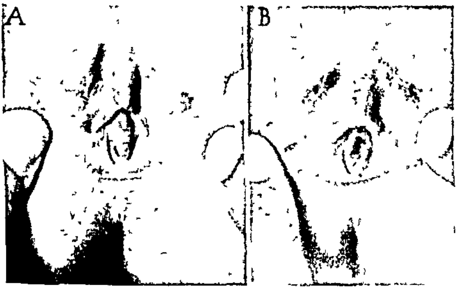

FIG. 1. Case 3. *A*, preoperative photograph showing mass protruding from urethra. *B*, urethral meatus 2 weeks postoperative. Area has completely healed.

clothes. Urinary symptoms or other complaints were absent. Examination revealed a dark, purplish-red mass protruding from the urethral meatus and almost completely filling the vaginal introitus. The mass was tender to touch and bled easily. A catheterized urine specimen, blood counts, Kahn test, excretory urogram and observation cystoscopy were all normal. The patient was first treated with hot sitz baths and on the third day, excision of the prolapsed mucosa was done with the cautery loop. No urinary symptoms developed and the child was discharged on the sixth day after surgery. On her last visit to the clinic, two months postoperatively, no stricture formation was noted. A No. 16 infant sound was easily passed into the bladder.

Case 5. *B. L., a 3 year old Negro girl, was admitted to the hospital with a history of bleeding from the vagina of 7 days' duration. She had no urinary complaints. The mother related that the child had sustained a hard fall on the floor 2 weeks previously. Nothing abnormal was noted at that time. Examination in the hospital revealed a prolapse of the entire circumference of the urethral mucosa through the meatus. The entire mass was acutely inflamed and completely obscured the meatal orifice. A splinter of wood was noted in the exposed mucosa and removed. The remainder of the physical examination was normal. A catheterized urine specimen, blood counts, Kahn test, observation cystoscopy and excretory urogram were normal. She was treated with hot sitz baths for 6 days and then the entire prolapsed mucosal cuff was removed with the cautery loop. No bleeding occurred. The patient was discharged on the third postoperative day. Her physician reported no stricture formation on the last examination which was made 4 months postoperatively.

Many predisposing and precipitating factors have been listed in the literature to explain prolapse of the urethra. In three of our cases a probable cause could be elicited. Strain from severe bouts of coughing was present in case 1: it was during a coughing spell that the mother first noted blood. Rape has been listed by Berry and Greene[4] as an infrequent cause of prolapse. In case 3, the mother first noted the swelling in the vagina soon after the patient was criminally attacked. Trauma was present in case 5; the finding of a splinter of wood embedded within the prolapsed mucosa supported this belief. No apparent etiological factor could be elicited in cases 2 and 4. It was apparent from the reports in the literature that many factors may produce prolapse of the urethra. Young girls having congenitally poor tissue structure locally or an abnormal mucosal redundancy are probably more susceptible to the development of prolapse of the urethra when they are exposed to such stress or straining factors as severe coughing, constipation or trauma.

The usual clinical findings have been urethral bleeding and the presence of a mass in the vaginal introitus. Urinary symptoms have been infrequent; when present, they were mild. In all our patients catheterized urine specimens and excretory urograms were done and found to be normal. In only one case was mild trigonitis noted on observation cystoscopy. The prolapsed mucosa surrounded the entire circumference of the meatus in all our cases.

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* A private patient of Dr. Merle Herriford who kindly allowed us to include this case in our report.

Many methods are available for the treatment of prolapse of the urethra Our procedure has been similar to that suggested by Moffett and Banks[1] Preoperative hot sitz baths are given for 3 to 5 days This helps in reducing some of the inflammation and aids in establishing a line of demarcation between the normal urethral mucosa and the inflamed prolapsed mucosa The surgical technique in removing the prolapse is simple The prolapse is put under slight tension by grasping anteriorly and posteriorly with two Allis forceps The cautery loop then quickly and completely removes the entire prolapsed urethra flush with its base at the line of demarcation No sutures are used to approximate the cut edges In none of our cases has it been necessary to use a catheter to control bleeding Little to no discomfort has occurred during the postoperative period On the day of discharge the urethra was dilated with infant sounds In the 3 and 4 year old patients a No 16 sound was used In the 8 year old girl a No 18 sound was used This was repeated weekly for two visits in the out patient clinic and then monthly for two or three visits In none of our cases did strictures develop

SUMMARY

Five cases of prolapse of the urethra in young girls are reported Complete circular amputation of the prolapsed mucosa with the cautery loop was found to be an effective and simple method of treatment The postoperative course of all our patients was surprisingly free of urinary symptoms There has been no evidence of postoperative stricture formation with this method of treatment

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TUBERCULOUS ULCER OF THE PENIS: PRIMARY SURGICAL EXCISION

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Penile tuberculosis is rare. In a recent complete review of the literature Lewis[1] found only 110 cases reported. Of these, 72 were the result of ritual circumcision in Jewish infants. Tuberculous affections of the penis have become singularly rare since the widespread adoption of surgical principles in circumcision. Aside from penile tuberculosis resulting from circumcision, Lewis found that the lesion was acquired either primarily as a result of coitus, fellatio or the wearing of infected clothing; or secondarily from tuberculous foci elsewhere in the body. The majority of the latter group were associated with urinary tract or seminal tract tuberculosis; only three cases having been reported in which the penis was involved following pulmonary tuberculosis without evidence of genito-urinary disease. The following case is reported because of successful surgical treatment of this rare condition.

W. T. (WGH 30196), a 38 year old white married machinist, entered the hospital on January 1, 1952 complaining of an ulcerated lesion on the shaft of the penis, which had begun 3 weeks earlier as a nontender superficial nodule. He could not recall any trauma or relation of the onset of the lesion to coitus. After incision by a local physician on the supposition that it was an abscess, the lesion rapidly ulcerated and enlarged.

The patient gave a history of hospitalization for 9 months in 1945 for pulmonary tuberculosis. Subsequent chest surveys, the last in October 1951, had revealed no evidence of activity. He denied cough, weight loss, fever, urinary symptoms or other systemic manifestations. His wife did not have tuberculosis and he denied extramarital sexual contact. There was no past history of venereal disease.

Examination revealed a healthy appearing, stocky young man. On the right side of the shaft of the penis there was a large ulcer measuring 4 by 4 cm. with raised undermined edges and a necrotic base covered with purulent exudate (fig. 1, *A*). The affected area was not painful or tender, and no inguinal adenopathy was present. The prostate, seminal vesicles and scrotal contents were normal to palpation and the prostatic fluid was of normal microscopic appearance. Blood count, sedimentation rate and urinalysis were normal. Chest films revealed minimal fibrosis in the right mid and lower lung fields, but were otherwise indeterminate. Excretory urogram showed normal upper tracts. Urine examinations were negative for acid fast bacilli on concentrated direct smear, culture and guinea pig inoculation. Extensive bacteriological studies were done without disclosing specific micro-organisms. Biopsy of the ulcer margin revealed a granulomatous lesion with no acid fast bacilli or spirochetes seen on special stains.

Accepted for publication February 27, 1953.

[1] Lewis, E. L.: Tuberculosis of the penis: A report of 5 new cases and a complete review of the literature, J. Urol., 56:737, 1946.

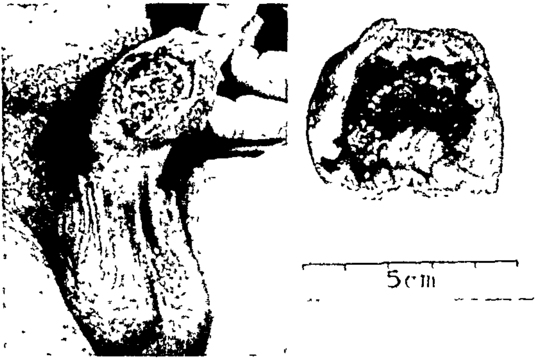

FIG. 1. Tuberculous ulcer of penis. A, at time of admission. B, surgical specimen following preoperative preparation.

The patient was treated on the dermatology service with sulfadiazine and chloramphenicol orally and with neomycin ointment locally. Following 7 weeks of this regimen the ulcer base became clean and presented healthy granulations, although the edges remained indurated and undermined. He was transferred to the urology service with a diagnosis of nonspecific granulomatous ulcer of the penis. Following additional local treatment with potassium permanganate soaks. the edges of the ulcer softened.

Because of the large defect present, surgical extirpation and plastic reconstruction were deemed advisable. The preoperative diagnosis was nonspecific granulomatous ulcer of the penis. The ulcer was excised with a 5 mm. skin margin between transverse elliptical incisions down to Buck's fascia (fig. 1, *B*). The ulcer base was moderately adherent but did not extend deep to Buck's fascia. For-

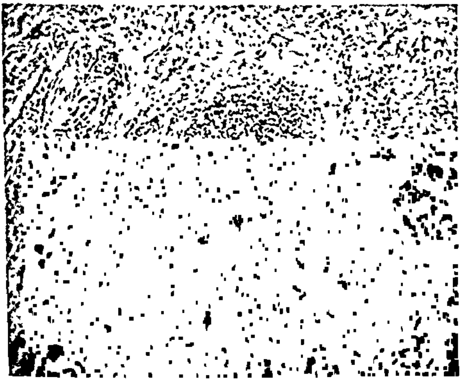

FIG. 2. Characteristic tuberculoid appearance. Acid-fast bacilli were found in Ziehl-Nielsen preparation.

tunately, the patient was not circumcised and therefore closure of the defect was readily achieved by retracting the prepuce, providing sufficient skin to slide over the shaft of the penis.

Microscopic examination revealed a tuberculoid granulatous base with numerous tubercle formations, giant cells and round cell infiltration. Acid fast bacilli were identified in the Ziehl-Nielsen preparation after intensive search (fig. 2).

Following the report of the tuberculous nature of the lesion, he was given streptomycin 1 gm. twice weekly and paraminosalicylic acid 12 gm. daily. The wound healed per primam, but the paraphimosis caused by the type of closure required a small dosal slit which corrected the constriction and edema. One month postoperatively the wound was entirely healed, and edema had abated (fig. 3). The patient was continued on streptomycin and paraminosalicylic acid therapy for 6 months, and the wound remained healed.

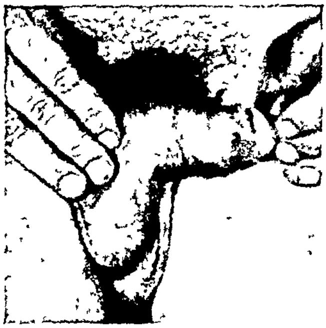

FIG. 3. Appearance of wound 6 months postoperatively

The patient has now been followed for 22 months since surgery and has remained well without recurrence of local or systemic tuberculosis.

DISCUSSION

The etiology of this tuberculous ulcer remains obscure. Studies were done on the patient's wife and no evidence of pulmonary or genital tuberculosis was found. Several possibilities exist as to its origin: that it resulted from contact with a partner having pelvic or pulmonary tuberculosis and was acquired in the act of coitus or fellatio; that it occurred as a result of re-inoculation by contact with his own infected sperm, urine or sputum in the vagina of his partner; or that it represents secondary hematogenous spread from his known but alleged inactive pulmonary disease or from his undisclosed genito-urinary tuberculosis.

The diagnosis in this case depended upon the finding of acid fast bacilli in the second surgical specimen referred for microscopic examination. However, the gamut of bacteriological investigations was helpful in ruling out other more common lesions of the penis.

Lewis states that the treatment of tuberculosis of the penis has been most unsatisfactory; that heat, ultraviolet, radiotherapy, chemicals and surgical excision have all been unsatisfactory by and large, and that generally the prognosis is quite poor. However, since the advent of recent tuberculostatic agents, the outlook has undoubtedly been altered. Excisional surgery and cure are now feasible in pulmonary, renal and seminal tract tuberculosis since miliary spread and local recurrence can be well controlled with streptomycin, paraminosalicylic acid and more recently, isoniazid drugs. It is therefore to be expected that similar treatment aimed at surgical cure will afford good results in large cutaneous tuberculous ulcers, and may indeed be the treatment of choice.

SUMMARY

A case of tuberculous ulcer of the penis is presented. The disease, although rare, has been recalcitrant in past reported cases. Successful surgical management of the case consisted in wide excision of the ulcer, plastic closure and maintenance of the patient with streptomycin and paraminosalicylic acid postoperatively. It is suggested that this may be the treatment of choice in tuberculous ulcers of the penis or of the skin elsewhere.

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IDIOPATHIC HEMORRHAGIC INFARCTION OF THE TESTICLE IN THE NEWBORN

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Hemorrhagic infarct of the testicle in the newborn infant is rarely recognized, and orchiectomy in the neonatal period is a rare surgical indication. This condition as seen in the first and second decades of life, however, is not uncommon and is most often the result of torsion of the spermatic cord. Testicular infarction has been reported as a complication of strangulated hernia in the infant[1] and has been noted as a result of torsion of the spermatic cord in the newborn.[2, 3, 4] However, the presence of hemorrhagic infarct of the testicle in the newborn has been observed in the absence of demonstrable evidence of torsion of the spermatic cord, hernia or trauma incident to labor. That this condition of complete gangrene of the testicle in the newborn can be a spontaneous development without predisposing factors or an antecedent exciting cause remains very questionable.

Five cases of hemorrhagic infarction of the testicle in the newborn due to torsion of the cord have been reported, and four cases of testicular infarct in the newborn, one by Campbell,[5] two by MacLean[6] and one by Ravich[7] with no demonstrable cause have been described. The fifth case of idiopathic hemorrhagic infarct of the testicle in the newborn is herewith presented.

The purpose of this paper is to specify the diagnostic criteria of infarct of the testicle in the newborn infant that have been thus far recognized in the relatively few cases which have been cited. This disease entity is apparently far more common than medical literature would indicate in view of the numerous instances of unexplained unilateral atrophy of the testicle as encountered in the adult. It is probable that the obstetrician, pediatrician and general practitioner in the past have encountered this condition which represented an obscure, benign, incomprehensible affection of the hemiscrotum which followed an uneventful course during the unknown process of aseptic testicular gangrene and atrophy.

CASE REPORT

Baby J. T. (No. 52-87), birth weight 7 pounds 7 ounces, was born at the Lutheran Memorial Hospital on January 27, 1952 of a 24 year old primipera

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Read before the annual meeting of the Medical Society of the State of New Jersey, Atlantic City, N. J., May 17, 1953.

[1] Rosenblatt, M. S. and Bueermann, W. H.: Strangulated hernia with acute hemorrhagic infarction of testicle in infants. Northwest Med., **38**: 18, 1939.

[2] Biorn, C. L. and Davis, J. H.: Torsion of the spermatic cord in the newborn. J.A.M.A., **145**: 1236-1238, 1951.

[3] Campbell, M. F.: Torsion of the spermatic cord in the newborn infant. J. Pediat., **33**: 323-327, 1948.

[4] Taylor, M. R.: A case of testicle strangulated at birth: Castration; recovery. Brit. Med. J. **1**: 458, 1897.

[5] Campbell, M. F.: Hemorrhagic infarction of the testicle in newborn. Pediatric Urology. New York: Macmillan Co., 1936, p. 113.

[6] MacLean, J. T.: Hemorrhagic infarct of the testicle in the newborn. Surg., Gynec. & Obst., **76**: 319, 1943.

[7] Ravich, R. A.: Hemorrhagic infarction of the testicle in the newborn. J. Urol., **57**: 875, 1947.

following normal labor, vertex presentation and spontaneous delivery. The mother who is a registered nurse examined the newborn infant within two hours after delivery and observed an enlargement of the left scrotum which was discolored and which did not arouse the infant on palpation.

Examination disclosed a smooth, nontender, globular, firm mass the size of a large green olive occupying the left scrotum, the wall of which was of bluish discoloration and nonedematous. The scrotal wall was adherent to the mass which was not in an elevated position in the scrotal sac. There was ample distance for palpation of the spermatic cord between the superior border of the mass and the external inguinal ring which was not dilated. There was nothing significant upon palpation of the left spermatic cord. The left scrotum did not transilluminate light. The right scrotal sac showed evidence of a small amount of hydrocele fluid. The right testicle was of normal size. A provisional diagnosis of left hematocele and right hydrocele was made.

On the fifth day of life incision and drainage of the apparent hematocele were decided upon since there was no change in the size or consistency of the scrotal mass. Without anesthesia an anterior longitudinal scrotal incision was carried through the scrotal tunics. The tunica vaginalis testis was entered and no bloody fluid or clot was present. A line of cleavage was obtained between the mass and the parietal layer of the tunica vaginalis with slight difficulty except at one area where a strip of capsule on the anterior border of the mass remained densely adherent to the parietal layer of the tunica vaginalis. The mass was dark red in color, symmetrical in contour and the size of a large green olive. The spermatic cord was glistening in appearance, was not discolored or edematous and entered

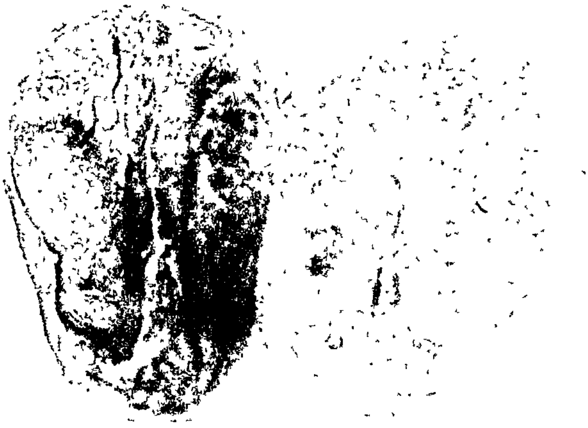

FIG. 1. Section of testicle shows marked enlargement, obliteration of parenchymal markings and mottled, hemorrhagic appearance.

the posterior border of the mass. The investment of the parietal tunica vaginalis was high on the spermatic cord. There was no gubernaculum or mesorchium. No twist in the intravaginal or extravaginal portion of the spermatic cord was demonstrable. The epididymis could not be identified. A longitudinal incision was then made into the mass on its anterior border to determine the presence of testicle within a possible organized hematocele clot. The entire surface of the cut section of the mass was firm, granular and dark red with no evidence of normal testicle. The cut section of the mass resembled an organized blood clot. No bleeding resulted from incision into the mass. The intravaginal portion of the spermatic cord was incised between clamps, and the mass and attached portion of the spermatic cord were removed. The postoperative course was uneventful, and the infant was discharged on the second postoperative day.

Pathological report (Dr. Edwin H. Albano): The testicle was enlarged and measured 4.9 cm. in its longest diameter (fig. 1). The surface was smooth and glistening except for small scattered tabs of pale yellow fatty tissue attached. The tunica was congested. On section the parenchymal markings are obliterated, and the tissue had a mottled, reddish-black, solid hemorrhagic appearance. Dark, thick fluid blood could be expressed from the cut surfaces.

Microscopic description (figs. 2 and 3): The chief pathological process was one of diffuse hemorrhagic infarction. The major portion of the testicular parenchyma was destroyed and replaced by extensive hemorrhage. Many of the erythrocytes lay in pools of edema fluid and laked blood. The few remaining tubules possessed a juvenile type of epithelium showing complete absence of spermatogenic differentiation. Some of the tubules had a pale, washed-out, ghost-like appearance.

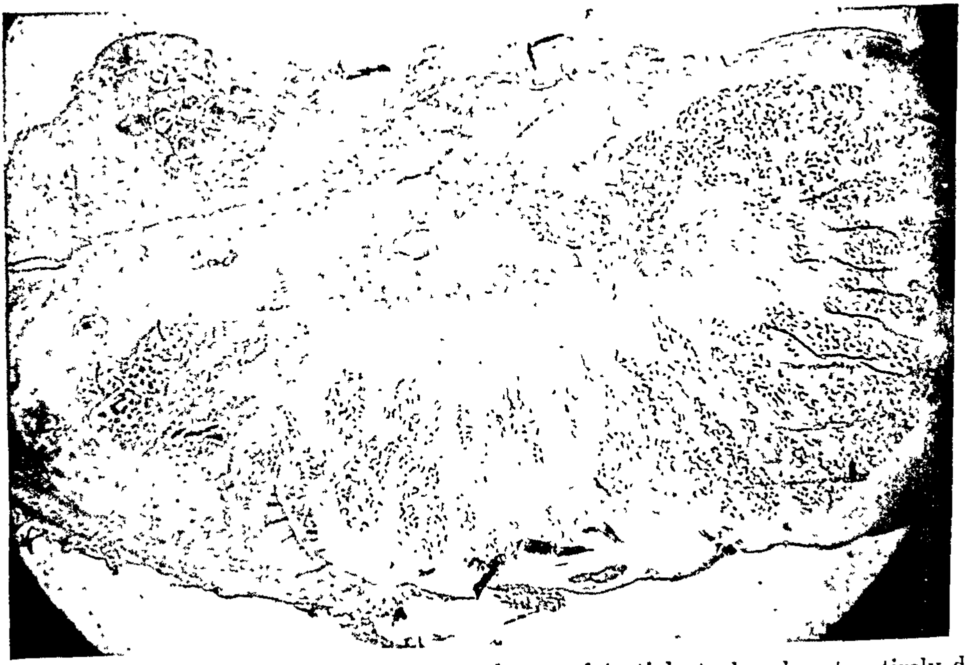

FIG. 2. Microscopic section reveals parenchyma of testicle to be almost entirely destroyed and replaced by extensive hemorrhage.

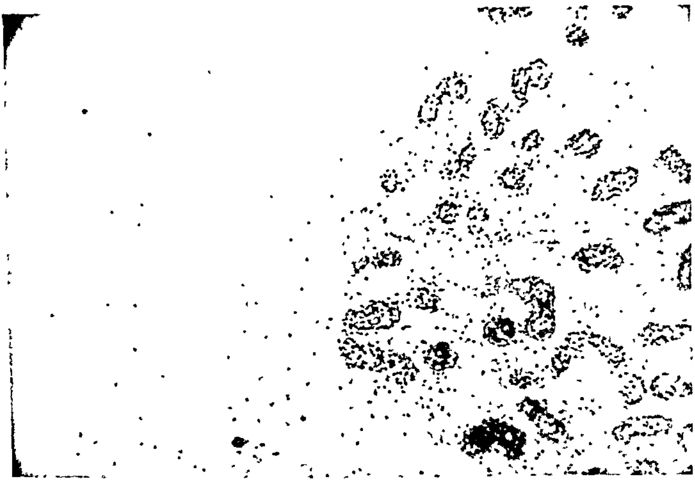

FIG. 3. Microscopic section discloses few scattered tubules that possess juvenile type of epithelium and complete absence of spermatogenic differentiation.

Bizarre tubular fragments and the remains of numerous pyknotic cell nuclei, as well as a few polymorphonuclear leukocytes and histiocytes, were scattered throughout. The tunica overlying the area of infarction was congested and necrotic. A moderate amount of fibrin was deposited in the adjacent tissue. Diagnosis: Hemorrhagic infarct of the testicle.

DISCUSSION

Bluish discoloration of a smooth, globular enlargement of the hemiscrotum is the outstanding clinical characteristic of idiopathic hemorrhagic infarct of the testicle in the newborn. The thin, delicate scrotal tunics of the newborn provide transparency to the purplish-red gangrenous testicle that is not usually seen in the child or adult. The degree of scrotal tenderness and edema would vary according to the time of occurrence of the process of hemorrhagic infarction during intra-uterine existence, labor or the neonatal period. Fever is mild. With the advance of time the scrotal wall becomes less edematous and is later adherent to the testicular mass which is firm and nontender.

The differential diagnosis of idiopathic hemorrhagic infarct of the testicle should be less difficult in the newborn than in infancy, childhood and adult life since epididymitis, orchitis and torsion of the spermatic cord and of the testicular and epididymal appendices are far more common after the neonatal period. Tumors of the scrotal contents, other than tumor testis, are very rare in the newborn. Tumor of the epididymis in the newborn has been reported.[8] The presence of scrotal masses requires consideration of such conditions as orchitis, due to mumps, trauma or syphilis, acute and chronic epididymitis, nonspecific, gonococcal or tuberculous, hydrocele and hernia. Testicular tumor, hematocele and hemorrhagic orchitis comprise diseases which are most difficult to differentiate.

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[8] Burros, H. M. and Mayock, P. P. Adenomatoid tumor of the epididymis Report of a case in a newborn. J. Urol., 63: 712, 1950.

Tumor testis presents unilateral discolored enlargement of the scrotum which might contain bloody fluid within the vaginal sac and is otherwise a firm, freely movable, nontender heavy mass. Supraclavicular lymph nodes and an epigastric mass may be palpable with x-ray evidence of lung metastases and positive Aschheim-Zondek test. Exploration biopsy may be the only possible method of diagnosis.

Primary or secondary hematocele is characterized by a smooth, globular, discolored mass which does not transilluminate light and often follows injury. Trauma incident to labor is not easily established in such cases.

Hemorrhagic infarct of the testicle due to torsion of the cord and spontaneous untwisting of the cord would be indistinguishable from idiopathic hemorrhagic infarct of the testicle since an elevated position of the testicle would not be present.

Hemorrhagic orchitis results from trauma to the testicle or interference with its blood supply. Obstetrical hemorrhagic infarction of the testicle may follow severe hemorrhagic or traumatic orchitis incurred during labor. The presence of a testicular mass at birth, however, would require serologic test to rule out syphilis and exploration biopsy to rule out neoplasm.

COMMENT

The pathological nature of this disease of the testicle in the newborn establishes a process of circulatory deprivation of the testicular parenchyma. In spite of the multiple source blood supply of the testicle no other parenchymatous organ is more vulnerable to acute complete circulatory occlusion and total necrosis. Although it is assumed that surgical untwisting of the spermatic cord within three hours from the onset of torsion will restore the blood flow to the testicle and salvage its structural and functional integrity it might not be presumptuous to regard occlusion of the vascular supply of the testicle in the newborn beyond fifteen minutes as capable of producing irreversible damage to the testicle.

Etiology of this condition is probably related to topographical variations of the scrotal contents. It is not without significance in the case herein cited that the parietal layer of the tunica vaginalis testis was found invested high on the spermatic cord, that there was present a long intravaginal segment of the spermatic cord and that there was no gubernaculum or mesorchium. Pathological evidence of organization of the inflammatory process within and about the testicle and adhesions of nonedematous scrotal tunics would place the onset of the process of infarction during intra-uterine existence or during labor which was uneventful. The diagnostic problem that presents in such cases demands surgical intervention not only for the purpose of possibly decompressing an hematocele to spare the testicle from pressure atrophy or performing orchiectomy for hemorrhagic infarct but for the purpose also of accomplishing exploration biopsy or orchiectomy in the possible presence of testicular tumor.

SUMMARY AND CONCLUSIONS

Bluish discoloration of a smooth, globular enlargement of the hemiscrotum is the outstanding clinical characteristic of idiopathic hemorrhagic infarct of the testicle in the newborn

Hematocele and testicular tumor are difficult to differentiate from hemorrhagic infarct of the testicle

Surgical exploration is indicated for the purpose of accurate diagnosis and accomplishment of required surgical treatment

The etiological basis of the development of testicular infarction probably lies in the anatomical variations of the scrotal contents Trauma, exertion, labor, inguinal surgery and the presence of inguinal masses provide influences which when superimposed upon topographical deviations of the testicle, spermatic cord and their tunics are capable of invoking complete or temporary circulatory occlusion of the vascular channels and irreversible damage to the testicle

Obstetrical hemorrhagic infarction of the testicle during the process of normal labor is apparently far more common than is generally appreciated and probably accounts for many cases of unexplained testicular atrophy seen in the adult

The fifth case of hemorrhagic infarct of the testicle in the newborn in the absence of a demonstrable cause is reported

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EPIDERMOID CYSTS OF THE TESTICLE

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From March 1951, through January 1953, eighty cases of testicular tumor were treated in the urological service of Walter Reed Army Hospital. Two cases of epidermoid cysts of the testicle and one of adult teratoma were included in this series. The latter is reported because it clinically resembled and was grossly largely composed of an epidermoid cyst. A review of the literature reveals that only five cases of epidermoid cysts of the testicle have been reported. One was reported by Dockerty and Priestley[1] in 1942, one by Gage and Brodie[2] in 1950, two by Mooslin and Schulte[3] in 1951, and one by Jensen[4] in 1952. Although the pathology has been well described, the etiology is still in controversy.

All testicular tumors are considered malignant until proved pathologically to be benign. In the following cases a diagnosis of benign tumor was made on the basis of bimanual palpation of the testicle. The tumors were small, ovoid, discrete, smooth, firm, and slightly mobile within the testicle.

In each case surgery was carried out through a scrotal incision. After removal of the tumor from the testicle, the tunica albuginea was approximated and the scrotum closed with drainage.

CASE REPORTS

Case 1.—A 29-year-old white man was admitted to Walter Reed Army Hospital on March 8, 1951. The patient had noticed a firm nodule in his left testicle for 5 years. Because of tenderness in the testicle of a few months' duration he reported to the hospital. Physical examination was unremarkable except for the nodule in the superior pole of the left testicle. Incision of the tunica albuginea revealed a 1.2 cm. firm tumor well encapsulated in a glistening white membrane and which easily shelled out of the surrounding normal testicular tissue. On section, the tumor contained a pale tan material arranged in concentric lamellae. Microscopic sections (fig. 1, *A*) revealed a cyst in which most of the wall was denuded, but where it was present it consisted of squamous epithelium. The lumen of the cyst contained keratin. The pathological diagnosis was epidermoid cyst of the testicle.

Case 2.—A 24-year-old white man was admitted to Walter Reed Army Hospital on October 20, 1952. A few days earlier while the patient was being processed for discharge from the Army, the examining physician found a nodule in his right testicle. This nodule had not been noticed by the patient nor had it caused symptoms. Physical examination was unremarkable except for the nodule in the superior pole of the right testicle. Incision of the tunica albuginea revealed a

Accepted for publication June 25, 1953.

[1] Dockerty, M. B. and Priestley, J. T.: J. Urol., **48:** 392–400, 1942.

[2] Gage, A. A. and Brodie, E. L.: J. Urol., **63:** 539–541, 1950.

[3] Mooslin, K. E. and Schulte, J. W.: Calif. Med., **74:** 435–437, 1951.

[4] Jensen, O. J. Jr.: J.A.M.A., **149:** 109–113, 1952.

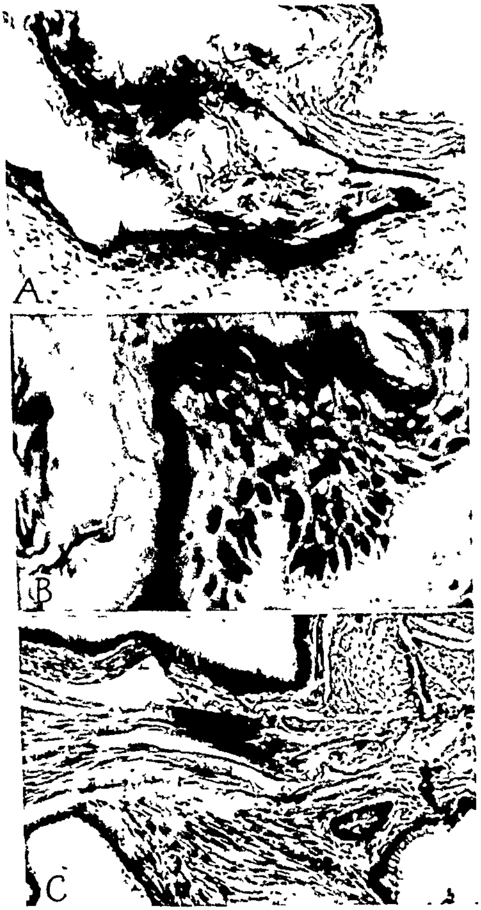

FIG. 1

1.2 cm. white, firm, smooth, ovoid tumor which was easily shelled out of the surrounding normal testicular tissue. On section, the wall of the cyst measured less than 1 mm. in thickness and contained a yellowish friable looking material. Microscopic sections (fig. 1, *B*) revealed the lining of the cyst to be composed of a thin layer of squamous epithelium. The squamous epithelium was clearly demarcated from the surrounding normal testicular tissue by a thin layer of fibrous tissue. The lumen contained keratin. The pathological diagnosis was epidermoid cyst of the testicle.

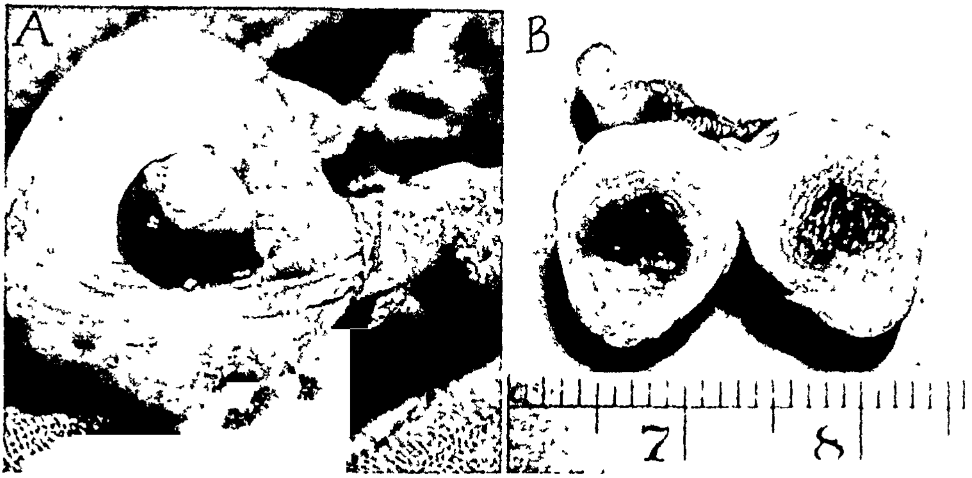

FIG. 2

Case 3.—A 22-year-old white man was admitted to Walter Reed Army Hospital on January 17, 1953. The patient had noticed a small nodule in his left testicle one year prior to admission. This nodule was found during a physical examination for a regular Army commission and the patient was referred to the hospital. Physical examination was unremarkable except for the nodule in the medial and superior portion of the left testicle. Incision of the tunica albuginea (fig. 2, *A*) revealed a 1 cm. white, ovoid, firm tumor which was well encapsulated and easily shelled out of the surrounding normal testicular tissue. At one edge of the tumor (fig. 2, *B*) was a cystic structure measuring 0.5 cm. in length. On section, the larger cyst contained a laminated yellowish-tan material, in the center of which was a brown discoloration. The smaller cyst contained a lipoid-mucoid material. Microscopic sections (fig. 1, *C*) revealed the lining of the larger cyst to be squamous epithelium with a granular cell layer. The content of the cyst was laminated keratin. The smaller cystic structure was composed of cysts lined by ciliated respiratory-type epithelium and mucus secreting intestinal-type epithelium. The pathological diagnosis was adult teratoma of the testicle.

SUMMARY

Two cases of epidermoid cysts of the testicle and one case of adult teratoma of the testicle have been presented because of their rare occurrence.

The authors are indebted to Col. Joe M. Blumberg, chief of pathology, Walter Reed Army Hospital for the microscopic descriptions of the tumors.

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SCLEROSING LIPOGRANULOMA OF THE SPERMATIC CORD

LOWRAIN E. McCREA

Sclerosing lipogranuloma is considered to be a peculiar granulomatous reaction in the fatty tissues. Ash and Friedman first called attention to the condition affecting the organs of the genito-urinary system, and called the condition sclerosing lipogranuloma. In 1948 Powell and Powell presented a case affecting the genitalia. Smetana and Bernhard in 1950 presented a classical description of the condition, reviewed the literature and presented 7 cases. Since 1950, two other investigators have presented cases typical in the histological picture, bringing the total number of cases affecting the genito-urinary system to thirteen, including the case to be presented. It is the purpose of the presentation to consider sclerosing lipogranuloma as it affects the spermatic cord and to review the literature of the condition as it affects the organs of the genito-urinary system. It has also been established that sclerosing granuloma is not always confined to the organs of the genito-urinary system but is known to occur in many other structures.

Because of the peculiar tissue reaction, the condition has been called by various terms, among which are saponifying necrosis, necrosis of subcutaneous fat tissue, ischemic fat necrosis, lipogranuloma, lipodystrophy, lipophages granuloma, adiponecrosis, lipoid necrobiosis. The term sclerosing lipogranuloma as used by Ash and Friedman is now considered standard.

The pathogenesis of sclerosing lipogranuloma is not known. The condition is believed to usually follow trauma. Grossly, the pathological appearance, according to Smetana and Bernhard, is characterized by disruption of adipose tissue, the presence of cystic spaces of various sizes filled with fluid or fatty material and scarring of varying density. These investigators conclude that following trauma "the essential consequence is not physical disruption but rather transformation of physiologic fat into a mildly irritating unphysiologic substance with which the body can cope only by transportation, segregation, and walling off from the normal tissue."

Analysis of the history of the cases presented and the microscopic specimens revealed that sclerosing lipogranuloma is a reaction of adipose tissue to trauma which is utterly different than the reaction of other tissues to trauma. Analysis further reveals that several had a definite and direct history of trauma while others presented a case history of a local inflammatory reaction. All cases showed a definite tendency to progress once the inciting element of the granulomatous reaction was established. Whether or not this reaction of adipose tissue is the result of a temporary interference of local blood supply and fat metabolism is not clear. It is established that lipogranuloma tends to continue when the process is once inaugurated. Spontaneous healing is slow and it is doubtful if it ever occurs. Undoubtedly this continued advancing process accounts for the

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Read at annual meeting, Mid-Atlantic Section, American Urological Association, Roanoke, Va March 12-14, 1953 numerous discordant interpretations of the physical and pathological findings that have been presented by numerous investigators.

The condition has been observed in the white and colored races and in both sexes. The age of the individuals affected varies in the reported cases from 20-60 years. Duration from onset to operation varies from 3 weeks (the case herein reported) to 8 years. Analysis of the reports in the literature reveals that the condition has affected the tissues of the scrotum in 3 instances; the penis twice; the scrotum and penis on 2 occasions; the epididymis, perineum, and the periurethral tissues once. Ordinarily tissue reaction quite quickly follows trauma. However, it will be noted that in some instances of sclerosing lipogranuloma, the condition has been slowly progressive for a period of years. Regardless of its position it has been shown that an inherent tendency to progress exists and there is only one method of treatment, namely, excision.

There is one important factor regarding sclerosing lipogranuloma that is yet to be explained. Trauma to adipose tissue is common, while the occurrence of sclerosing lipogranuloma is relatively rare. Therefore, basically, there must be some underlying inherent causative factor, accompanying trauma or inflammatory reaction producing the condition.

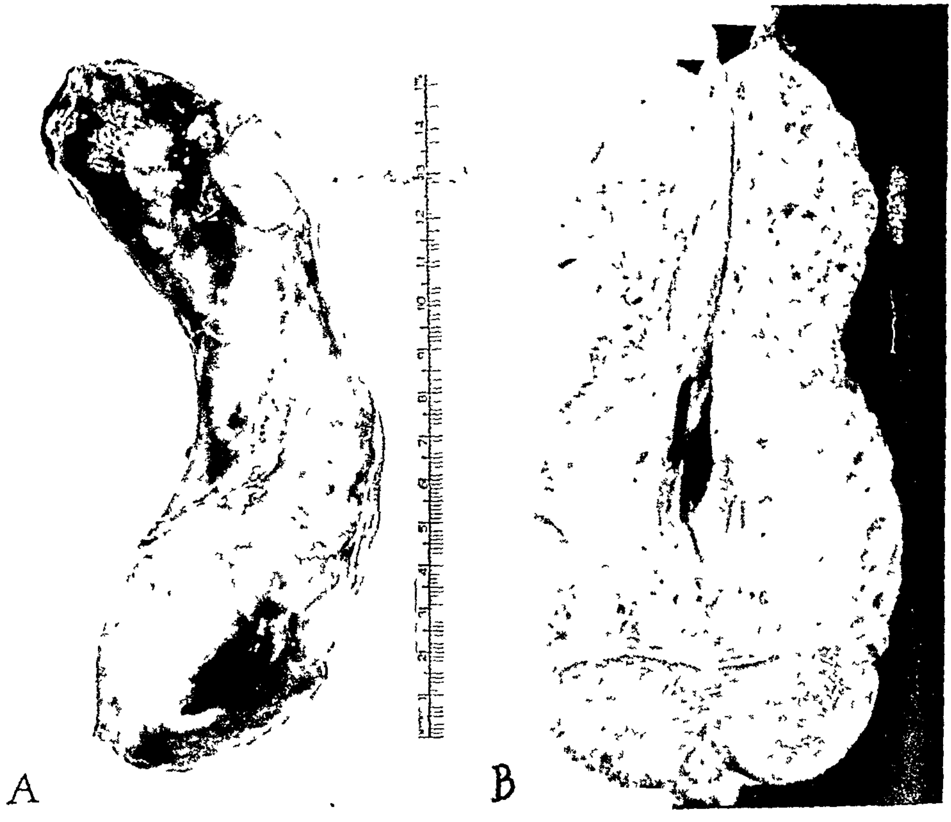

FIG. 1. *A*, large, cylindrical, painless mass extending from internal inguinal ring into scrotum Mass, although movable, appeared fixed to surrounding tissue *B*, note almost complete obliteration of structures of spermatic cord by fatty tissue Testicle appears grossly normal

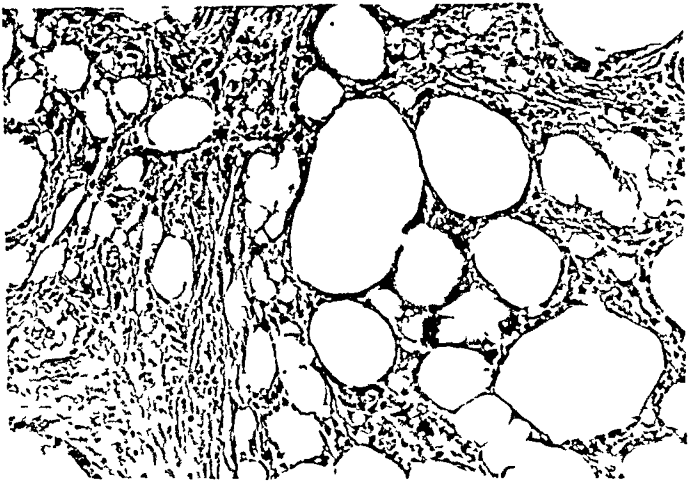

Fig 2 Background of fibrofatty tissue Fat lobules are distorted and in some areas disclose microcystic dilatation Microcysts are lined by lipid laden macrophages or giant cells of foreign body type Stroma is sprinkled by lymphocytes macrophages, eosinophiles and giant cells

CASE REPORT

A white man 59 years of age was re admitted to the hospital 3 months following abdominoperineal proctosigmoidectomy for carcinoma of the sigmoid There was present a painless, increasing, cylindrical mass involving the left spermatic cord (fig 1, A) This mass was not apparent before proctosigmoidectomy It was first noticed 3 weeks following surgery The patient refused intervention for the removal of the mass at that time, but as the mass continued to increase in size he agreed to surgery for its removal (fig 1, *B*) The spermatic cord was ligated at the level of the internal inguinal ring and the mass including the testicle was bluntly dissected from the scrotum The postoperative course was uneventful Diagnosis Sclerosing lipogranuloma of the spermatic cord (fig 2) This patient was seen February 2, 1953, eight months following the removal of the sclerosing lipogranulomatous mass, at which time a hard, cylindrical mass was palpable at the internal inguinal ring This mass, according to the patient, is not painful but is gradually increasing in size

SUMMARY

Sclerosing lipogranuloma is a reaction of fatty tissue which occasionally follows trauma The process of the reaction is not known but is believed due to interference of local blood supply and fat metabolism Spontaneous healing of sclerosing lipogranuloma is slow, if it ever occurs Once established there is an apparent tendency to continued progression. The only known treatment for sclerosing lipogranuloma is excision. A review of the reported cases affecting the organs of the genito-urinary system is presented together with the addition of a personally observed case.

CONCLUSION

An apparent unexplained inherent causative factor accompanying trauma of inflammatory reaction tends to produce sclerosing lipogranuloma.

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SEMINAL TRACT CALCULI

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Several articles in the urological literature of the past 2 years have called attention to calcification of the seminal vesicles and ampullary portions of the vasa in association with diabetes mellitus. This calcification has been demonstrated to consist of calcific deposits or replacement within the muscular walls of these organs.

A careful search of the literature for at least the past 50 years, however, has failed to reveal a report of discrete calculi within the canals of the seminal tract. A short paragraph in Keyes' *Textbook of Urology* refers to "sandy" deposits found in the seminal vesicles in autopsy specimens but other than this no reference to seminal calculi can be found. It is my purpose here to report 2 cases of such "seminal calculi."

CASE REPORTS

Case 1.—Mr. F. Z. first presented himself in March 1942 at the age of 31 complaining of dull, aching suprapubic pain of 8 years' duration. Cystoscopic examination was negative except for evidence of posterior urethritis. Treatment with prostatic massage failed to give relief and, after a short time, treatment was discontinued. He re-appeared in October 1945 with the same symptoms plus a urethral discharge and terminal hematuria. The same diagnosis was made and the same treatment given. The urethral discharge and the terminal hematuria ceased but the suprapubic and perineal pain persisted. At this time a palpable calculus in the left side of the prostate was noted and confirmed by x-ray (fig. 1).

In March 1950 he was admitted to the hospital for surgical removal of this calculus. At this time, on cystoscopic examination, it was noted that pressure over the stone by a finger in the rectum caused a jet of bloody material to escape from the orifice of the left ejaculatory duct. The bladder and upper urinary tract were normal except for duplication of the left kidney pelvis and ureter.

The prostate was exposed through a perineal incision and the large stone was readily palpated in a superficial position in the left half of the gland. An incision was made over it and it was removed. It was noted that it lay in a cavity which appeared to be lined with mucous membrane and it was found that a probe could be passed readily in both directions from the cavity. There seemed little doubt but that this stone lay in a greatly dilated portion of the left ejaculatory duct.

The perineal wound healed cleanly and he was discharged from the hospital on the seventh postoperative day.

For about 6 months he was completely free of symptoms but the dull suprapubic ache recurred and had continued intermittently to date of admission although never so severe as before the stone was removed. Recent x-rays had shown no evidence of recurrent calcification and a seminal vesiculogram showed

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Read at a meeting of the New England Section, American Urological Association, April 30, 1953.

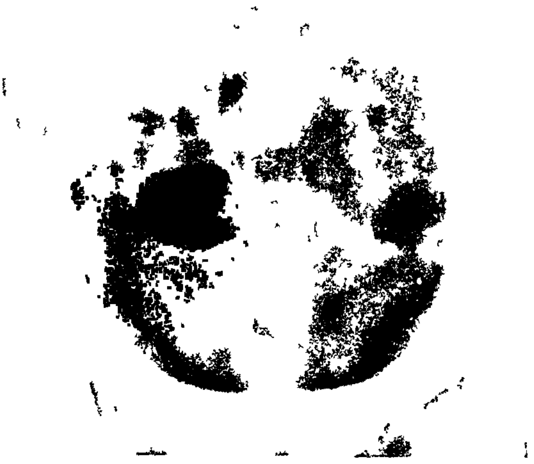

Fig. 1. Case 1. Large calculus in prostatic area which proved to be within ejaculatory duct.

free drainage from both sides with apparently normal seminal tracts. The prostatic secretion became normal and a semen specimen was normal in all respects.

Case 2—P. D. was a 20 old boy when he first came under observation in February 1948. At that time he was admitted to the Hartford Hospital with a story of acute onset of very severe right abdominal pain. He was writhing all over the bed, retching, vomiting and complaining of agonizing right abdominal pain which seemed colicky in nature. There was marked right abdominal spasm and tenderness and some tenderness in the right costovertebral angle. His white blood count was 12,000, 84 per cent polymorphonuclear neutrophils. His urine contained 3–5 red blood cells per high power field. There was slight right rectal tenderness. The presumptive diagnosis was right ureteral colic but an excretory

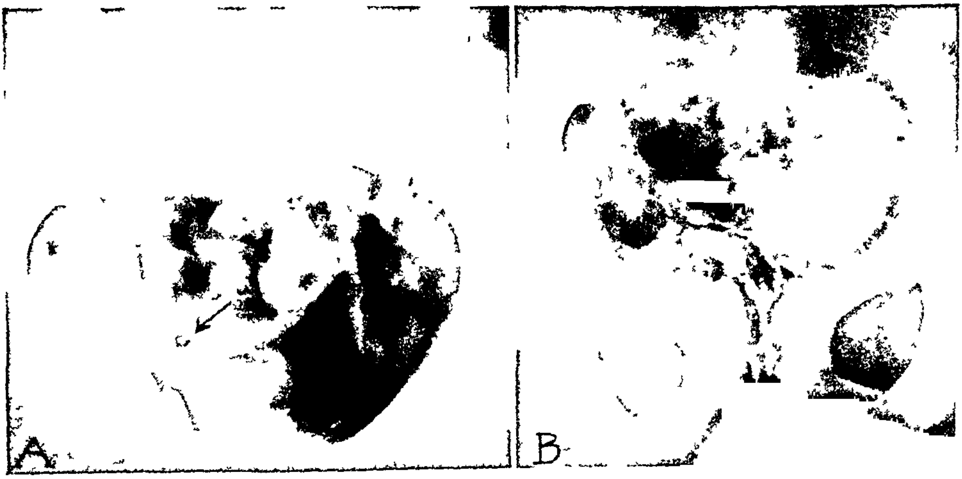

Fig. 2. Case 2 *A*, right ureterogram made with occluding catheter in ureteral orifice and demonstrating calcific shadow medial to, and definitely outside ureter *B*, right seminal vesiculogram showing sacculation of ampulla of vas at level of tip of vesicle and indistinct filling defect in saccule

urogram was negative and an appendectomy was done with removal of a normal appendix. The surgeon who treated him at that time felt when he discharged him that he had probably had a right ureteral calculus that had passed spontaneously.

In July 1948, five months later, he was re-admitted for study with the story that he had continued to have attacks of right abdominal pain 5 or 6 times a month. These attacks were always acute in onset, bore no relation to any particular sort of activity and lasted usually a day or two. They continued to be very severe. Cystoscopy showed acute and chronic posterior urethritis, normal upper urinary tracts with a calcific shadow in the right side of the pelvis which was definitely extra-ureteral (fig. 2, *A*). Chest x-ray was negative. Barium enema, gastro intestinal series with small bowel studies and cholecystogram were negative. It was observed that there was a little thickening in the region of the right seminal vesicle and definitely increased tenderness here. Treatment by prostatic massage and vesicular stripping gave no relief and was discontinued after a trial.

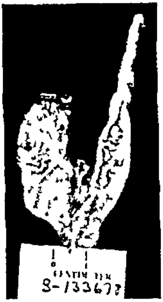

FIG. 3. Case 2. Right seminal vesicle and ampullary portion of right vas deferens with calculus.

During the next 3 years the patient was at college in Vermont and was seen only rarely though he continued to have attacks of severe colic at irregular intervals. These were of such severity that he usually landed in a hospital where the work up was inconclusive and the attack subsided. At various times he was studied at several large hospitals and at least two famous New England diagnostic centers. He returned finally to Hartford where recurring attacks of pain often called his doctor out in the middle of the night to administer sedatives. By this time the young man began to feel that his future was being blighted by this mysterious malady that kept him from work for a day or two several times a month. His doctor, on the other hand, was torn between a certainty that there was an organic cause for the symptoms and a growing conviction that he was dealing with a bizarre manifestation of psychoneurosis.

In February 1952, four years after the first attack, the patient was again admitted to the hospital for study. By this time it seemed probable that the symptoms were due to chronic seminal vesiculitis with an exaggerated reaction to pain. He was again subjected to complete diagnostic study. A psychiatrist felt that he was a normal young man who was only justifiably worried by his infirmities. A seminal vesiculogram showed an essentially normal seminal tract on the right side except for a peculiar sacculation in the ampulla of the vas that was at first thought to be of little importance (fig. 2, *B*). Puzzling over the problem one day, the forgotten "extra-ureteral calcific shadow in the right side of the pelvis" came to mind and, when a film in which this shadow appeared was superimposed on the right seminal vesiculogram, the shadow fell into the sacculation of the ampulla of the vas and the diagnosis of vasolith was made.

The right seminal vesicle, together with the ampullary portion of the right vas with its contained stone, was removed through a perineal approach (fig. 3). The wound healed well. The patient was discharged in 10 days and in a year and a half he has had no more pain, he has been married and he has this month become a father.

In both of these cases diagnosis and definitive treatment were too long delayed because of ignorance of the possibility of seminal calculi. With the knowledge of the possibility of having stones in the seminal tract one can be sure that pelvic "phleboliths" will be viewed with a little more suspicion in obscure cases henceforth. In like fashion one could criticize the vasectomy and vesiculectomy in the second case when it is quite possible that vasolithotomy alone would have sufficed. The only defense again is ignorance of the disease process and the desire to insure relief from recurrent painful and disabling episodes in a young man who was rapidly reaching the end of his endurance.

One can only speculate on the subject of etiology. The stone in the second case was analyzed and found to consist of carbonate apatite (carbonated calcium phosphate). It would seem likely that inflammation or congestion had prompted bleeding with retention of a small clot which became calcified instead of being evacuated or absorbed.

In conclusion, 2 cases of obscure abdominal pain due to discrete calculi in the seminal tract have been described. So far as can be determined this entity has not previously been reported.

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CORTISONE THERAPY IN OSTEITIS PUBIS

C. A. HOFFMAN AND R. F. ERHARD

Osteitis pubis was first described as an entity by Edwin Beer in 1924. In 1945 Muschat reported a series of 25 cases collected from the literature and reported with these his own 2 cases. The great majority of these followed prostatectomy by the suprapubic route, however, others have reported the development of osteitis pubis following other operative procedures. Wilensky reported 2 cases in women, one which followed a symphysiotomy and the other appeared after a normal delivery. A vaginal fistula developed originating at the os pubis. In a third case appearing in the female, the clinical picture of osteitis pubis was reported by Klemberg. This infection was apparently metastatic, the source being pyelonephritis.

In 1923 Barnes reported the clinical picture of osteitis pubis following a perineal prostatectomy. The clinical picture has also been reported following an infected inguinal hernia repair. Wheeler, in 1941, reported extensive invasion of the os pubis following suprapubic cystostomy. The clinical picture has also been found with a prostatic abscess, and with occupational trauma to the lower abdomen.

Following Millin's introduction of prostatectomy by the retropubic approach in 1946, osteitis pubis became one of its accepted hazards. Beneventi, a staunch advocate of this procedure, suggested that this complication may be due to disturbance of the blood supply to the os pubis. Most workers agree that the two requisites for this clinical picture are trauma and infection. The large percentage increase in this complication following the advent of retropubic prostatectomy lends support to this view. The case of trauma to the periosteum of the pubis while working in the limited prevesical space is obvious. Great care must be used in the handling of retractors and surgical needles. The ever present infection in any prostatic surgery is the second requisite.

PATHOLOGY

Although many workers have studied the pathology of osteitis pubis, the picture is still not clear. Goldstein, by means of a biopsy of the pubic bone, in one of his cases, described the pathology as showing the presence of loose cellular connective tissue within the marrow spaces. This connective tissue was infiltrated with polymorphonucleocytes, lymphocytes, and a few histiocytes. The fragments of bone at biopsy were softer than those of normal bone. The pathological diagnosis was reported as "fragments of bone showing a histologic picture compatible with the diagnosis of osteitis."

Pierson reported biopsy of the bone in one of his patients as showing a chronic inflammatory reaction. Silver reported his biopsy as showing a nonspecific acute, inflammation. Wheeler, however, was of the opinion that osteitis pubis is a result

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Read at annual meeting Mid Atlantic Section, American Urological Association, Roanoke, Va., March 12–14, 1953.

of nerve injury. He reported one case in which at autopsy there was no inflammatory process, but an atrophy of the cellular elements of the bone was found. Osteitis pubis was classified by him as a form of Sudeck's atrophy. This atrophy originally was described by Sudeck in 1900.

SYMPTOMATOLOGY

Clinically, the symptoms rarely appear less than 10 days following surgery, and usually within 2 to 6 weeks. The symptoms are manifested by a gradual onset of pain and tenderness over the body or rami of the pubis or ischium. This is followed by pain along the inner and outer aspects of the thighs and occasionally in the perineum. There is increasing pain in the groins on walking and later painful spasm of the adductor muscles of the inner thigh. The patient usually is confined to bed. There may be painful defecation or urination due to spasm of the levator ani and levator perinei, both of which are attached to the periosteum of the pubis. The course is usually febrile, and persists for several weeks. The disease is self-limiting, the pain and tenderness usually lasting from six to eighteen months.

RADIOLOGY

Radiologically, there may be no findings in the early stages. The first noticeable change is a fuzziness or haziness in the pubis or its rami. This is followed by a frayed appearance of the periosteum, most commonly along the descending rami. This is followed within 2 or 3 weeks by a moth-eaten appearance of bone destruction in the pubic rami. In late stages there may be a separation of the symphysis due to a destruction of the cartilage. Healing may be characterized by spur formation, ossification of the symphysis, or by healing and restitution of new bone.

TREATMENT

Since recognition of osteitis pubis as an entity, different clinicians have suggested various types of treatment. Most workers agree that until the advent of adrenocorticotrophic hormone (ACTH) and cortisone, all of the recommended treatment left something to be desired. Treatments in vogue were diathermy, radiation therapy, chemotherapy and antibiotics. On the presumption that osteitis pubis was a trophic disease, large doses of vitamin B complex have been used. Frequently orthopedic treatment such as splints, traction, novocain injection, obturator crush, and physiotherapy have been beneficial in relieving pain. Hock and Kurtz stress the importance of removal of foci of infection. This is done by lavage of prevesical space with solutions containing antibiotics either by introduction through a catheter or needle. Recently Marshall and his group have reported encouraging results from ACTH. Daw also reports gratifying results with the use of cortisone.

CASE REPORTS

Case 1. A 65 year old Negro was first seen in January 1952 with symptoms of prostatism. Urological studies revealed benign hypertrophy of the prostate and stricture of the anterior and membranous urethra A flat radiograph of the abdomen, at that time, did not reveal any disease of the bones of the lower abdomen and pelvis Transurethral prostatectomy was performed and the patient made an uneventful recovery The urethral stricture was dilated in early May and on June 1 in the office Following the second dilatation, the patient returned to his home in a nearby town. Subsequently acute urinary retention developed His physician unsuccessfully attempted to pass a catheter and he was referred to the hospital in acute urinary retention

On admission the clinical picture was that of urinary extravasation A suprapubic cystostomy was done and an indwelling urethral catheter inserted The suprapubic tube was removed 4 days postoperatively and the urethral catheter removed 5 days later. He had an uneventful postoperative course and returned home on June 29, 1952 Six days later he was again admitted to the hospital complaining of marked pain in the right inguinal region, groin, and both testicles The pain was sufficiently severe to prevent him from walking

On physical examination the positive findings were tenderness on light pressure over the pubic bone and lower abdomen This was accompanied by pain on adduction of both thighs His temperature was 99 8F The urinalysis showed a trace of albumin and microscopically revealed many red blood cells His blood studies were essentially normal except for a hemoglobin of 65 per cent and a red blood count of 3,200,000

The clinical picture was one of osteitis pubis The patient was immediately placed on 300,000 units of duracillin daily and 0 5 gm of dihydrostreptomycin twice daily intramuscularly This was supplemented by sulfamerazine by mouth and diathermy to the painful area After approximately 2½ weeks of this therapy only slight improvement was noted both objectively and subjectively At that time all therapy was discontinued A flat radiograph of the lower abdomen was reported as showing multiple confluent areas of bone destruction of the bodies of both pubic bones adjacent to the symphysis involving especially the posterior halves of both pubic bodies (fig 1, A) He was then placed on cortisone· 300 mg the first day, 200 mg the second day and 100 mg daily for 10 days After a few days of this therapy, the patient began to improve markedly At the end of the 12 days of cortisone therapy he was free of pain, his temperature was normal, and there was no evidence of tenderness on pressure over the involved areas See figure 1, *B*

After completion of cortisone therapy a re-examination of the lower abdomen was done by radiograph which was reported as showing complete regeneration of both pubic bones without residual areas of bone destruction The patient was discharged 3 days later apparently free of all symptoms of osteitis pubis He was advised to return for follow-up urethral dilatation This advice he has not followed

Case 2 This case report is offered by Dr R M Bobbitt et al A 74 year old white man underwent a suprapubic prostatectomy for benign hypertrophy of the prostate on September 22, 1952 Four weeks following surgery pain developed

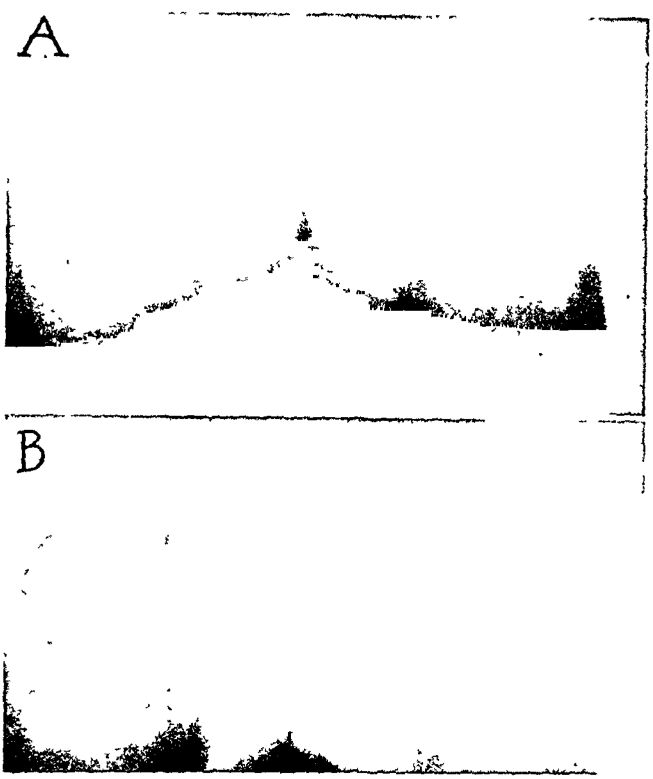

FIG. 1. Case 1. *A*, x-ray several weeks after suprapubic cystotomy for ruptured urethra and day prior to cortisone therapy. Marked decalcification of both pubic bodies, more marked adjacent to symphysis, with complete destruction of medial cortex of both pubic bodies. *B*, after 12 days of cortisone therapy. Complete regeneration of both pubic bodies except for small triangular destroyed area in right superior pubic body.

in the pubic region and thighs, and the patient had difficult in walking. The clinical picture of osteitis pubis progressed rapidly. The adductor spasm became so marked that the thighs could not be separated. A flat radiograph taken on December 17, 1952 revealed the moth eaten appearance of the pubic rami, consistent with a diagnosis of osteitis pubis.

The patient was placed on cortisone therapy, 100 mg. for 2 days, followed by 50 mg. a day for 1 week, then 25 mg. a day for 30 days. Within 24 hours after beginning cortisone, marked subjective improvement followed. The patient was able to walk without pain after 3 days of treatment. After 10 days of cortisone he was free of symptoms.

DISCUSSION AND CONCLUSION

A brief review of the literature on osteitis pubis has been given. Two additional cases are reported because of dramatic response to cortisone therapy. The diagnosis was confirmed by radiographic evidence. The first case also was of interest because of its unusual causative factor. The second case was of interest because of the rapid disappearance of subjective complaints.

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CARCINOMA IN MALDESCENDED TESTES

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We wish to report 3 cases of carcinoma occurring in undescended testes. One of these, torsion of an intra-abdominal testicle with associated malignancy, is of particular interest because of the few cases published.

CASE REPORTS

Case 1. R. O., Mercy Hospital No. 6410, a 20 year old white man, was seen on October 12, 1950 because of sudden excruciating pain arising in the lower left quadrant and radiating to the scrotum and left thigh. Since the onset of the pain, the patient had not been able to urinate. There was no history of previous urinary difficulties.

On physical examination, the abdomen was acutely tender and rigid in the lower left quadrant. The left testicle was not present either in the scrotum or inguinal canal. The patient was catheterized with ease and 1½ ounces of clear urine obtained. Urinalysis and complete blood count were normal. Kahn test was negative. A plain x-ray showed the kidney and psoas shadows to appear normal. No evidence of calculus was seen.

A diagnosis of torsion of an intra-abdominal testicle was made. Through a left pararectus incision the peritoneum was opened, and a torsed mass, the size of an orange, was found overlying the bladder. An epididymis-like structure and a vas deferens were present in a small peritoneal pouch occupying the left portion of the scrotum. The tumor mass, epididymis and peritoneal pouch were removed en masse.

Pathology report: The oval encapsulated testis measured 10 cm. by 5 cm. and was composed of soft, gray, hemorrhagic, sarcomatous-appearing tissue without any normal architecture apparent. The attached cord-like structure showed several dilated and thrombosed veins. The essential lesion of the testis was a markedly anaplastic carcinoma of the embryonal type. The tumor cells in many instances appeared to practically line blood filled spaces within the substance of the tumor. The testicle had been almost completely replaced by tumor which had even invaded the epididymis. Diagnosis: Embryonal carcinoma of testicle (Dr. David A. Todd, San Antonio).

Postoperatively the patient was given deep roentgen therapy. Chest film done October 28, 1952 was normal. The patient has remained in good health to date.

Case 2. A. S., Mercy Hospital No. 6556, a 34 year old white man, was admitted October 26, 1950, because of a tender mass in the right groin of 2 to 3 months' duration which originally had been diagnosed as epididymitis of an undescended testicle. Under penicillin therapy the tenderness decreased, but the mass had shrunk only slightly in size. In addition dysuria, urinary burning and a small urinary stream were present. Gonorrhea occurred many years ago. In 8 years of married life, his wife had never become pregnant.

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On physical examination, the right testicle was present within the inguinal canal, was three times normal in size and acutely tender. The left testicle was not palpable. The external urethral meatus was small. A urethral stricture 5F in size was present one inch within the external meatus. The prostate was boggy. Urinalysis was normal. Complete blood count: Red blood cells 5,350,000, hemoglobin 14.2 gm., white blood cells 15,450; neutrophiles 79, lymphocytes 20, eosinophiles 1. Kahn test was negative. Chest film was normal.

A diagnosis of bilateral undescended testicles and possible right testicular tumor was made. A left inguinal incision was made, and a small, soft, flabby testis was found at the level of the internal ring. The cord was freed of adhesions, and sufficient length was obtained to place the testicle within the scrotum. A right inguinal incision was made. The cord was ligated and cut at the level of the internal ring, and the testicle removed. The urethral stricture was cut to size 30F following which a 28F sound could be passed with ease. A urethral catheter was left indwelling.

Pathology report: The testicle formed an oval, flattened mass measuring 9 by 7½ by 4 cm. There was a segment of vas deferens 6 cm. in length. The opened cut surface of the testis was found to contain a soft, necrotic, mottled, hemorrhagic tumor mass which measured 7 by 6 by 4 cm. The periphery was formed by the capsule and some fibrous thickening. The epididymis did not appear to be grossly involved and measured 3 by 1½ by 0.7 cm. The tumor of the testicle was a markedly anaplastic embryonal carcinoma which had practically destroyed all testicular tissue. The tumor was markedly necrotic in some areas with associated hemorrhage and what appeared to be infection. The epididymis was involved as was also the first portion of the spermatic cord. Diagnosis: Embryonal carcinoma of the testicle (Dr. David A. Todd).

Postoperative deep x-ray therapy was given. On March 19, 1951, the patient complained of hemoptysis, weakness, pain in the back of the head, and dizziness. Chest film showed a lesion 3 cm. in diameter in the second left anterior interspace. Additional deep x-ray therapy plus teropterin were given. The patient steadily declined and expired April 29, 1951. Permission for autopsy was not obtained.

Case 3. J. G., Mercy Hospital No. 7349, a 28 year old white man, was seen January 6, 1951, with the following history: Four days previously, while doing heavy lifting, the patient felt pain in the right testicle. That evening the pain became worse, and he had a low grade fever. A diagnosis of epididymitis was made, and penicillin given. Tenderness, however, persisted. In 1944 an operation had been done because of bilateral cryptorchidism. The right testicle had been brought into the scrotum; the left removed because of insufficient length of cord.

On physical examination well healed, bilateral inguinal scars were present. The right testicle was tender and slightly enlarged. It was thought that the epididymis was twice normal in size though a line of demarcation between testis and epididymis could not be felt. Urinalysis was normal. Complete blood count: Red blood cells 4,890,000, hemoglobin 13.5 gm., white blood cells 11,600; neutrophiles 75, lymphocytes 23, eosinophiles 2. Serology was negative.

A preoperative diagnosis of traumatic epididymitis was made. The scrotum was incised, and its contents evacuated. The testis was twice normal in size, bluish-black in color and quite hard. The epididymis was only slightly enlarged. The testicle was removed.

Pathology report: The specimen consisted of a markedly enlarged nodular testicle measuring 5 by 3 by 3 cm. The testicle was practically replaced by lobulated tumor of a solid structure and encephaloid appearance. Sections from the testicular tumor showed it to be typical embryonal type of carcinoma with heavy infiltration of stroma by lymphocytes. The tumor had practically replaced all of the testicular tissue although no serosal infiltration was seen. In areas the tumor has undergone marked necrotic changes. It had spread through into the epididymis which showed a right large tumor composed of embryonal cells. Diagnosis: Embryonal carcinoma of testicle involving epididymis (Dr. David A. Todd).

Postoperatively a course of deep x-ray therapy was given. Chest films have remained negative for metastasis, and the patient is in apparent good health.

DISCUSSION

Campbell states that failure of normal descent of the testicle occurs in 1 to 3 per cent of males. In 10 per cent of these it is bilateral. The proportion of abdominal to inguinal testes is 1:4. Descent usually takes place in the first year. If it has not done so by puberty, it is unlikely to occur.

A variety of pathological conditions are associated with cryptorchidism. More than 70 per cent have a concomitant inguinal hernia. Practically all postpubertal cryptorchid testes are sterile because of the heat factor (Moore). In addition atrophy due to interference with circulation, compression within the canal or to trauma may take place. Meyer reported 3 cases of fatal peritonitis due to suppurative epididymitis in abdominal testes.

Torsion of an intra-abdominal testicle is rare. Charendoff et al. found 19 cases in the literature and added one. Malignancy was present in 65 per cent of these.

Various authors have stated that the incidence of malignancy in cryptorchidism is 20 to 40 times as great as in normally descended testes. Moreover the chances of an abdominal testicle becoming malignant are greater than that of one retained within the inguinal canal. Whether all undescended testes are potentially malignant remains a controversial issue.

In 3½ years of private practice the author has seen 5 cases of malignancy of the testes. Three of the five were in undescended testes. One case of malignant degeneration took place 7 years after orchiopexy. Cabot believes that successful orchiopexy reduces the danger of malignant deterioration.

In view of the poor prognosis for undescended testes as to spermatogenesis, incidence of infection, trauma, and malignant degeneration, it behooves us to study this problem with care. In all probability undescended testes should be brought into the scrotum surgically at or before puberty if no response is obtained with hormone therapy. Testes which cannot be placed within the scrotum should be removed. It is suggested that surgical correction done some time after puberty does not reduce the possibility of malignant degeneration.

SUMMARY

Three cases of carcinoma in undescended testicles are reported. One was discovered concomitantly with torsion of an intra-abdominal testicle. Another occurred 7 years after orchiopexy.

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FATAL REACTION FOLLOWING AORTOGRAPHY WITH NEO-IOPAX

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With the progressive refinement of injection techniques, administration of radio-opaque media has become a frequent diagnostic procedure. Because of increasing numbers of cases studied, toxic or allergic reactions may be encountered. To prevent repetition of serious or fatal reactions, as well as to assist in evaluation of new products, it becomes the duty of the physician promptly to report the occurrence of all untoward reactions. The product Neo-Iopax (Disodium N-methyl-3, 5-diiodo-chelidamate) has enjoyed a widespread acceptance in the field of excretory urography. Instances of allergic and other reactions to this material have appeared in scattered reports[1-8] in the literature. Reference[9] was made to a fatality resulting from the use of pyelectan in an editorial but the case was not described in detail. The following case is presented as an example of a fatal reaction to Neo-Iopax.

CASE REPORT

M. S., a 35 year old white woman, was first seen in May 1952 by one of us (A. J. J.) with the complaint of palpitation and headaches in early morning. She reported a systolic hypertension of 200 mm. of mercury known since September 19, 1951. She had been told during her pregnancy twelve years earlier that her blood pressure was elevated "slightly."

The blood pressure was 190 mm. of mercury systolic and 120 mm. diastolic. Examination of ocular fundi revealed moderate diffuse arteriolar sclerosis without exudates or hemorrhages. The optic discs appeared normal. No other physical findings of note were encountered.

Blood nonprotein nitrogen, complete blood count, serologic test for syphilis and electrocardiogram were negative or within normal limits. Roentgenogram of the chest was normal. Serum albumin was 3.6 gm. per 100 cc; serum globulin was 3.4 gm. Urinalyses revealed specific gravities of 1.008 and 1.009 with albuminuria ranging from trace to 2 plus. An excretory urogram made with 20 cc of a 50 per cent solution of Neo-Iopax revealed absence of visualization of the

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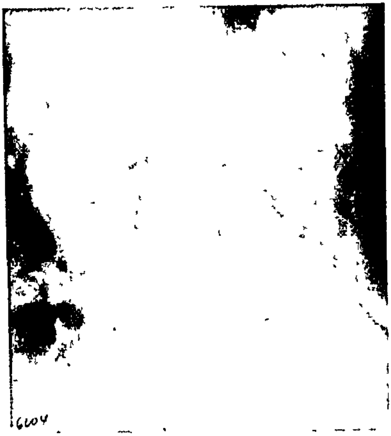

FIG. 1

left kidney with a large ureteral calculus measuring 1.2 cm. in diameter located at the ureterovesical juncture. There was a compensatory hypertrophy of the right kidney. Serum calcium and phosphorus were within normal limits and phenolsulphthalein excretion was 64 per cent in 2 hours.

Removal of the left kidney was contemplated because of its possible contribution to the vascular hypertension resulting from renal ischemia (Goldblatt effect). It was necessary to obtain an estimation of the circulatory status of the kidney before concluding that nephrectomy was indicated. Accordingly, on July 11 an aortogram was made through the translumbar approach. Neo-Iopax (15 cc of a 75 per cent solution) was used as a contrast medium. The procedure was performed with ease and the patient complained of no discomfort at the time. The renal arteriogram obtained is reproduced in figure 1. The day after this procedure the patient complained of nausea, vomiting, edema of the face and neck, and diffuse myalgic pains.

Because of protracted vomiting and a persisting ileus, the patient was hospitalized on July 16. The temperature was elevated to 100–101F during the first 3 days of hospitalization. Initial laboratory data revealed mild anemia and normal values for serum electrolytes. The blood nonprotein nitrogen was 120 mg. per cent. Bleeding time was reported as 21 minutes. The patient's symptoms persisted and the urine became grossly bloody; the volume averaged 200–500 cc daily. The oliguria persisted in spite of the administration of intravenous fluid in amounts calculated to replace fluid and electrolyte losses and to correct dehydration without producing edema. The hospital course was stormy and the patient did not respond to supportive therapy, which included blood transfusions, antibiotics and fluid and electrolyte replacement. The azotemia progressed with the blood nonprotein nitrogen stabilizing in the range of 580 mg.

per cent. The ileus was refractory to treatment. A terminal uremic pericarditis and diffuse petechial rash appeared and she died the twenty-sixth day.

At necropsy, the findings of note were confined to the lungs, heart and kidneys. Approximately 1500 cc of blood tinged fluid was present in the left pleural cavity and 1000 cc in the right cavity. The lungs weighed 800 gm. There was partial atelectasis of both lower lobes. The pericardial sac contained 500 cc of thin bloody fluid. A shaggy fibrinous red gray exudate was present on epicardial and pericardial surfaces.

The heart weighed 375 gm. Left ventricular hypertrophy was marked, the wall measuring 17 mm. in thickness. The endocardium was thin and smooth and there were no valvular defects. All major coronary arteries were patent and no significant atherosclerosis was observed.

The left kidney was a scarred, shrunken, nodular organ measuring 6 by 4 by 3 cm. Its slightly thickened capsule stripped with moderate difficulty leaving a pitted surface on which there was a solitary thin walled cyst 12 mm. in diameter. The sectioned surface revealed marked dilatation of the pelvis and all calyces. The entire parenchyma measured less than 5 mm. in thickness. At the left ure-

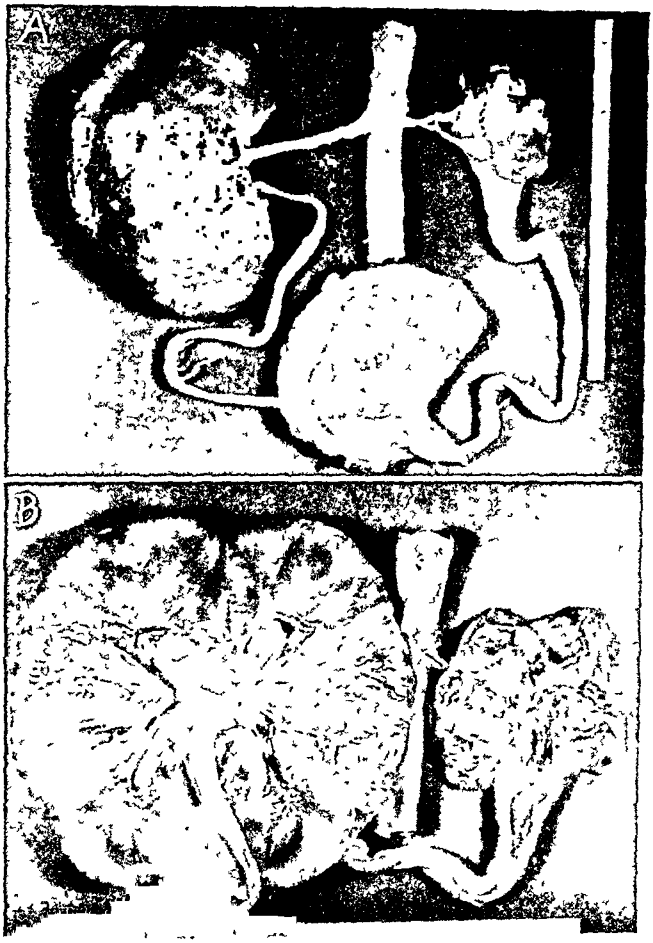

Fig. 2

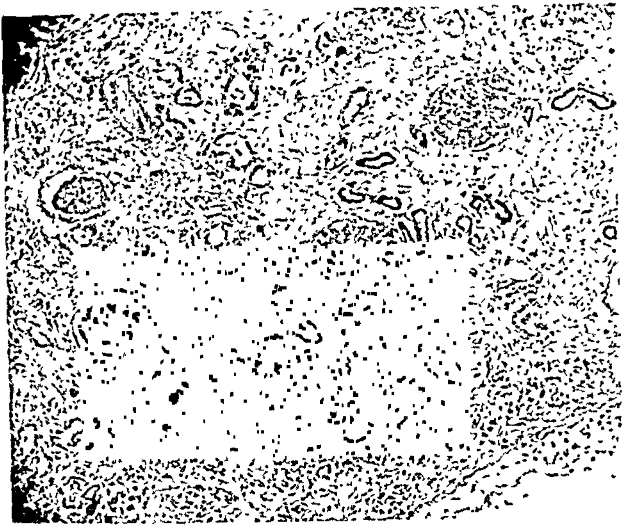

FIG. 3

terovesical juncture a dark brown stone measuring 1.2 by .8 cm. completely obstructed the ureteral ostium.

The right kidney extended nearly to the pelvic brim and measured 15 by 8 by 7 cm. A thin capsule stripped with ease leaving a soft, flabby, mottled, yellow-grey surface studded by soft, cortical abscesses measuring 1 to 3 mm. in diameter. Numerous pinpoint areas of hemorrhage were also observed scattered over the cortical surface. Similar hemorrhagic areas also were seen in the sectioned surface throughout the cortex and miliary abscesses up to 1 cm. in diameter were found in the medullary portions and tips of the pyramids. The ureter appeared normal. The kidneys and bladder are reproduced in figure 2.

Microscopic sections of the left kidney revealed findings consistent with advanced stage of severe chronic pyelonephritis. Findings in the right kidney are represented in figure 3. Several distinct processes were apparent as represented by multiple small abscesses, intimal fibrosis involving arterioles and small arteries, infarction of glomeruli with hemorrhage into the capsular spaces, and various stages of tubular destruction and regeneration. In many of the proximal convoluted tubules there were marked destruction and desquamation of lining epithelium. Regenerating flat, darkly staining, newly formed epithelial cells were seen in numerous tubules.

COMMENT

This is a case of hypertensive cardiovascular disease associated with an atrophic left kidney secondary to chronic hydronephrosis and pyelonephritis. In spite of a diffuse nephrosclerosis the contralateral kidney exhibited only moderate impairment of function until a severe insult precipitated renal failure. Clinically this reaction followed and was apparently produced by an aortogram in which Neo-Iopax was used. Because of facial edema, prolonged bleeding time, and severe gastro-intestinal disturbance, it was presumed that the episode was produced by an allergic response to the dye. However, the anatomical changes found in the glomeruli and tubules of the right kidney suggested a severe toxic reaction, such as that which may be seen with acute heavy metal poisoning. It is true that a high concentration of the dye probably entered the right kidney, as revealed by the roentgenogram. This may be attributed to the absence of circulation in the left kidney and perhaps also to the fortuitous placement of the needle in the aorta exactly opposite the lumen of the right renal artery. This however, was the purpose of the procedure technically and should not pose an undue hazard for the patient or a penalty for the physician.

Though there were advanced vascular changes in the right kidney, this patient might still have enjoyed a favorable response following a left nephrectomy. Instead a fatal reaction following the use of Neo-Iopax occurred.

SUMMARY

An aortogram, in which Neo-Iopax was used, apparently produced a toxic reaction which was fatal to a patient with hypertensive cardiovascular disease associated with one atrophic kidney. Reports indicate that nonfatal untoward reactions to Neo-Iopax are not uncommon. This case is presented to indicate this dye may also be lethal in its effects.

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THE CLINICAL USE OF CYCLAINE (HEXYLCAINE) AS AN ANESTHETIC AGENT IN UROLOGICAL SURGERY:—A REPORT OF OBSERVATIONS OF 1000 PATIENTS

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Hexylcaine (1-cyclohexylamino-2-propylbenzoate) was synthesized by Hancock, et al 1944.[1] Its possible clinical use was suggested by animal studies conducted by Beyer, et al. 1948.[2] They showed the compound to have an order of toxicity comparable to procaine, an order of topical anesthesia comparable to cocaine, an order of nerve block anesthesia intermediate between butacaine and tetracaine, and a duration of spinal anesthesia second only to tetracaine (over twice as long as procaine).

There followed a preliminary clinical report of its usefulness by Ruben and Anderson 1949[3] who observed 400 patients in whom cyclaine anesthesia was used. They concluded, "our experience to date indicates that the new drug provides complete and longer lasting nerve block in smaller doses relative to its animal toxicity than does procaine." Torkelson and Cooley 1951[4] reported on its use in low spinal anesthesia in obstetrics in 1000 patients They were impressed by the uniformly satisfactory anesthesia obtained and "the large percentage of patients in whom there was no appreciable lowering of blood pressure." According to Orkin and Rovenstine 1952,[5] cyclaine in 1 per cent solution is stable to boiling and autoclaving for sterilization purposes The solution is stable for one or more months with no apparent loss of effectiveness

Our observations were begun July 1952 and continued for one year. During this time cyclaine anesthesia in one form or another was given to 1000 patients. Types of anesthetic techniques and numbers of patients involved are presented in table 1.

CYCLAINE FOR CAUDAL ANESTHESIA (320 PATIENTS)

A solution of cyclaine in the concentration of ½ of 1 per cent was used for all caudal anesthesias The dosage was 30 to 40 cc. In figure 1 the technique of single dose caudal anesthesia is illustrated Figure 2 shows an actual dissection of the caudal canal with relationship of the caudal needle to the cauda equina

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Sharp and Dohme, Inc , Philadelphia, Pa furnished cyclaine (hexylcaine) for this investigation

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TABLE 1. *Types of cyclaine anesthetic techniques*

	NUMBER OF PATIENTS
Caudal	320
Continuous caudal	75
Hyperbaric spinal	140
Hypobaric spinal	25
Topical: female bladder and urethra	75
Topical: male urethra	225
Local infiltration	140

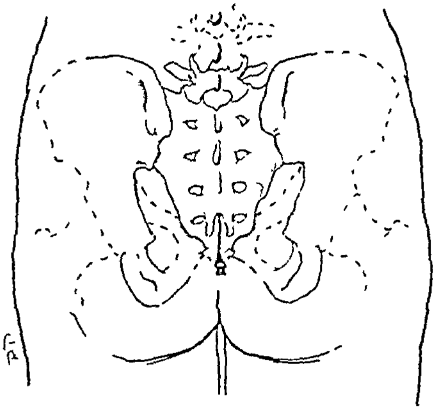

FIG. 1

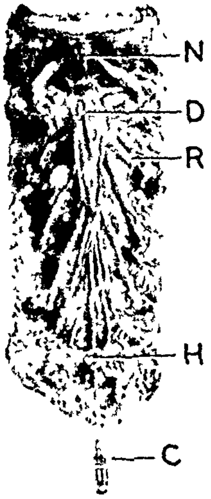

FIG. 2

FIG. 1. Schematic anatomical presentation of technique of single dose caudal anesthesia; No 19 needle in caudal canal.

FIG. 2. Photograph of actual dissection of caudal canal showing in detail: *N*, spinal cord; *D*, dura; *R*, nerve; *H*, hiatus of caudal canal; *C*, No. 19 caudal needle.

In table 2 the various procedures done under single dose caudal anesthesia are enumerated.

In this series of 320 single dose caudal anesthesias surgical anesthesia was obtained in 3 to 7 minutes and remained profound for the duration of the procedure. No supplemental anesthesia was necessary. There were no untoward reactions.

CYCLAINE FOR CONTINUOUS CAUDAL ANESTHESIA (75 PATIENTS)

A solution of cyclaine in the concentration of ½ of 1 per cent was used for all continuous caudal anesthesias. The initial dose was 80 cc, supplementing as needed during the course of the surgery. Only five of the patients required any supplemental administration of the agent. In figure 3 the technique of continuous caudal anesthesia is illustrated. In table 3 the procedures done under continuous caudal anesthesia are enumerated.

Anesthesia was profound and satisfactory for the duration of the procedure

TABLE 2. *Procedures done under single dose cyclaine caudal anesthesia*

	NUMBER OF PATIENTS
Cystoscopy, ureteral catheterization and retrograde pyelography	231
Cystoscopy	70
Transurethral resection of prostate	3
Circumcision	3
Ureteral dilatation	2
Internal urethrotomy	2
Transurethral fulguration	2
Urethral dilatation	2
Litholapaxy	1
Meatotomy	1

in every patient. One patient had a mild transient loss of consciousness shortly after injection of the cyclaine solution, but recovered in about 5 minutes.

CYCLAINE FOR HYPERBARIC SPINAL ANESTHESIA (140 PATIENTS)

A solution of cyclaine in the concentration of 1 per cent in 5 per cent dextrose was used for all "low spinals." Four to five cubic centimeters of the solution (40 to 50 mg. of cyclaine) were used. The specific gravity of this hyperbaric solution was found to be 1.0200 (spinal fluid is 1.0060). In table 4 the procedures done under this method of "low spinal" are enumerated. In all instances the solution was injected intrathecally without dilution with spinal fluid, the pa-

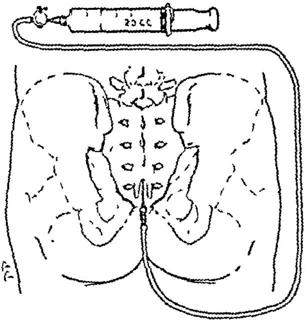

FIG. 3. Schematic anatomical presentation illustrating technique of continuous caudal anesthesia. No. 19 malleable steel needle in caudal canal and connected to supply of ½ of 1 per cent cyclaine solution in syringe.

TABLE 3. *Procedures done under continuous caudal anesthesia using cyclaine*

	NUMBER OF PATIENTS
Perineal prostatectomy	72
Total radical prostatoseminalvesiculectomy	3

TABLE 4. *Procedures done under hyperbaric spinal cyclaine*

	NUMBER OF PATIENTS
Transurethral resection of prostate	74
Transurethral fulguration of bladder tumor	24
Cystoscopic manipulation for ureteral calculus	15
Cystoscopic examination with retrograde pyelography	4
Litholapaxy	4
Cystoscopy	4
Internal urethrotomy	4
Excision urethral lesions	4
Meatotomy	2
Orchidectomy	2
Transurethral endovesical ureterolithotomy	1
Circumscision	1
Excision of spermatocele	1

tient being in sitting position during injection and for three minutes following injection.

In all instances the anesthesia was rapid in onset (3 to 5 minutes), profound, and of a duration sufficient for the operative procedure. No supplemental anesthesia was necessary and there were no untoward effects.

CYCLAINE FOR HYPOBARIC SPINAL ANESTHESIA (25 PATIENTS)

A solution of cyclaine in the concentration of ¼ of 1 per cent was used for all hypobaric spinal anesthesias. This solution was prepared by diluting 1 cc of 5 per cent cyclaine with sterile distilled water to a volume of 20 cc. The hypobaric solution thus prepared contains 2.5 mg. of cyclaine per 1 cc and has a specific gravity of 1.0028 (spinal fluid is 1.0060). The solution is injected intrathecally without dilution with spinal fluid with the patient in lumbar position, operative side up. We have preferred to inject through a Lemmon continuous spinal setup; in the event that the operation is prolonged, supplemental injections may be given. The dosage is 10 to 15 cc (25 to 37.5 mg). The technique is shown in figure 4. Anesthesia developed in 3 to 7 minutes after initial injection and was profound allowing completion of the surgical procedures without supplemental injection of solution. No untoward reactions occurred.

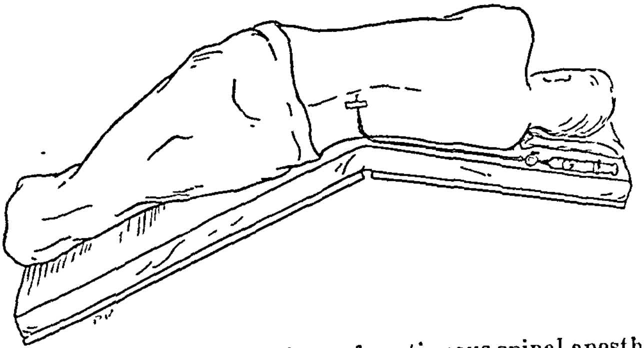

FIG. 4. Schematic presentation of technique of continuous spinal anesthesia using hypobaric cyclaine solution for lumbar surgical approach.

TABLE 5. *Procedures done under hypobaric spinal cyclaine*

	NUMBER OF PATIENTS
Nephrectomy	16
Ureterolithotomy	4
Pelvioplasty	2
Nephropexy	1
Pelviolithotomy	1
Nephrostomy	1

TOPICAL CYCLAINE ANESTHESIA OF THE FEMALE BLADDER (75 PATIENTS)

A solution of cyclaine in the concentration of 1 per cent was used for all topical cyclaine anesthesias of the female bladder. The bladder was drained with a small urethral catheter and 30 cc of the solution introduced. In table 6 the procedures done under this type of anesthesia are enumerated.

Anesthesia was almost immediate in onset and satisfactory for completion of the procedure. There were no untoward effects.

TABLE 6 *Procedures done under topical cyclaine anesthesia in the female*

	NUMBER OF PATIENTS
Cystoscopy, ureteral catheterization, and retrograde pyelography	68
Cystoscopy	7

TOPICAL CYCLAINE ANESTHESIA OF THE MALE URETHRA (225 PATIENTS)

A solution of cyclaine in the concentration of 5 per cent was used for all topical cyclaine anesthesias of the male urethra. Five cubic centimeters of the solution were introduced into the urethra with the 5 cc urethral tip glass Asepto syringe. The solution was retained in the urethra by finger pressure for a period of 3 minutes before beginning instrumentation. In table 7 the procedures done under this type of anesthesia are enumerated.

TABLE 7. *Procedures done under topical cyclaine anesthesia in the male*

	NUMBER OF PATIENTS
Cystoscopy	205
Urethral dilatation	20

TABLE 8 *Procedures done under local infiltration anesthesia with cyclaine*

	CC OF ½ OF 1% CYCLAINE	NUMBER OF PATIENTS
Bilateral vasectomy	5 cc each side	124
Circumcision	50 cc	4
Bilateral orchiectomy	30 cc each side	5
Suprapubic cystostomy	100–150 cc	3
Biopsy scrotal lesions	10–20 cc	2
Meatotomy	5 cc	2

Anesthesia was almost immediate in onset and satisfactory for completion of the procedure. There were no untoward effects.

LOCAL INFILTRATION ANESTHESIA WITH CYCLAINE (140 PATIENTS)

A solution of cyclaine in the concentration of ½ of 1 per cent was used for all local infiltration anesthesias. The amounts used in any one patient varied from 5 to 150 cc of solution. In table 8 the procedures done under this type of anesthesia are listed.

Experience with cyclaine as an agent for infiltration anesthesia impresses one with its almost immediate onset, excellent spreading factor, and depth of anesthesia. There were no serious immediate or delayed systemic reactions, or evidence of any acute or delayed local tissue damage or irritation.

SUMMARY

Cyclaine is an anesthetic agent with qualities suitable for use in infiltration, regional, and topical anesthesia. It possesses the advantages of rapid onset, prolonged activity, profound depth of anesthesia, and decreased toxicity.

It would appear clinically that cyclaine is less toxic than procaine and that cyclaine is a more satisfactory topical anesthetic agent in the bladder or urethra than 2 per cent cocaine.

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A NEW INTERCHANGEABLE TUMOR RESECTING INSTRUMENT

SAMUEL F. KRAMER

Neoplasms of the bladder have received intense therapeutic attention by all urologists in an effort to evolve the best surgical approach. Those who advocated the most radical surgical attack on all but the simple papillomas have had their opportunity to present their results. Likewise, the time honored results of destruction of papillary neoplasms of varying malignancy by physical agents have been impressed on urological thinking. The author, like all urologists, has considered his own experience and the published results of the great clinics.

Cystoscopic experience and acumen helped by biopsy must still be the greatest factor in choice of procedure. Surface malignancies which are papillary in type can be treated successfully and some permanently cured by physical modalities. Infiltrative papillary and nonpapillary lesions (neoplastic extension deeply into and beyond the muscularis) can not be cured by physical agents and few can be cured by the most radical surgical approach. However, partial and very radical cystectomy unquestionably have a definite place in the therapy of bladder neoplasm.

In 1936 the author presented a ball tipped interchangeable electrode to be used with a McCarthy electrotome and at that time predicted that the resectoscope was the most natural and precise instrument for the instrumental treatment of bladder neoplasm. His thought at the time was that a ball tipped electrode used at the base of a growth gave deep penetration of electrocoagulation where it was most needed. As the era of bold resection of the prostate advanced it was inevitable that bold electroresection of growths should have its trial. Extensive experience has demonstrated that electroresection of the mass of the growth is best and deep electrocoagulation of the base of the growth is desirable. Parallel clinical and pathological studies of excised neoplastic bladders revealed the limitation of both the physical and surgical treatments and may have served to stabilize urological thinking.

During instrumental resection of papillomatous growths, some of rather broad base, the loop of the resectoscope has sometimes failed to cut growths which were not fixed since the villi floated away from the loop. The author therefore presented to Mr. Frederick J. Wallace the idea which is hereafter described. If the instrument is worthy of gathering momentum it will be due to the genius and kind interest of a person who has already earned the most honored and revered regard of urologists everywhere.

Figure 1 reveals an interchangeable element which can be passed through a No. 28 resectoscope sheath. A spring maintains the cutting loop in the proximal position well inside the No. 28 sheath. Visualization is obtained with a No. 68 McCarthy panendoscopic telescope. Thumb pressure forward pushes the loop retrograde from the inside of the resectoscope sheath distally through the newly formed fenestra into the terminal recessed beak. Release of thumb pressure

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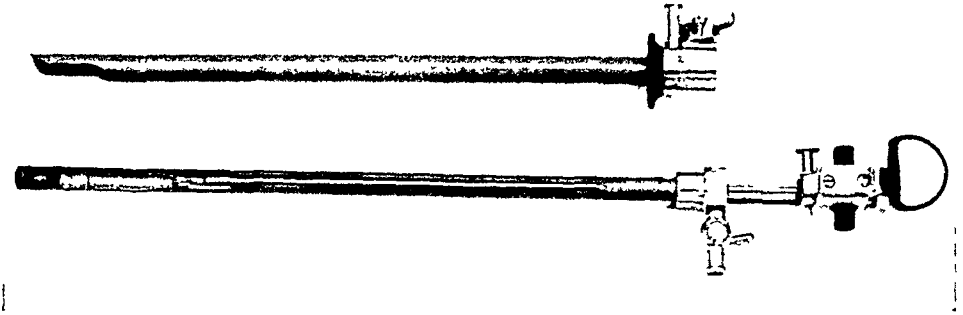

FIG. 1

permits the loop to be returned to its original position within the sheath. Thus tissue fixed between the loop moving retrograde and the terminal hollow, niched beak can be cut and if desired the loop returning to its original position may be activated by the cutting current for the purpose of resection.

The field of usefulness for such an interchangeable element should be greatest for certain types of neoplasms and also for retrograde resection of residual prostatic tissue close to the external sphincter during endoscopic resection of the prostate. In the latter instance the external sphincter may be protected from accidental injury.

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RENAL PAIN

AUSTIN I. DODSON

It is the purpose of this presentation to call further attention to a group of patients who complain of pain typical of that usually associated with disease of the kidneys and ureters without demonstrable pathological changes. Renal and ureteral pain is usually associated with obstructive lesions of the upper urinary tract, and one can usually demonstrate a stone, a stricture, stenosis of the ureteral orifice, a kink in the ureter, or ureteropelvic obstruction. Renal pain may also be associated with perirenal inflammation in tumors of the kidney, particularly when hemorrhage has occurred within the tumor, and with renal cysts.

We are occasionally consulted by patients who present none of these pathological processes, whose kidneys appear normal in outline, whose pelves and ureters have a configuration within normal limits, and in which function and emptying time is normal. Yet, the patient complains of constant or periodic pain that cannot be differentiated from the pain we commonly associate with demonstrable renal disease. These patients are usually women and the pain has its onset during the menstrual time of life. In most cases the patients are of a highly nervous temperament and in many instances such factors as economic insecurity, domestic or personal affairs further complicate the problem. The marital state does not seem to be significant. Of 8 patients reported by Crabtree, four were married. Young et al. reported 5 cases of nephralgia, two of whom were married, and of the four patients recorded in this report only one was single. In most cases the patient bears from one to several abdominal scars, the result of surgical efforts to restore her health.

In many instances the onset of pain follows rather closely some previous illness usually involving the kidneys or pelvic structures. One of my patients first suffered pyelonephritis following a pelvic operation. Two had been operated upon for renal ptosis and one had had bilateral renal calculi with the loss of one kidney. Delayed emptying of the renal pelvis without evidence of organic obstruction is occasionally encountered, and minor degrees of renal mobility are not unusual. In some cases the ureterogram presents a straight, narrow tube as evidence of ureteral spasticity.

L. S. Young, W. E. Wilson and R. Nelson in the *Journal of Urology* (May 1950) in a discussion of nephralgia present an excellent description of the autonomic nervous system as related to renal pain. A brief abstract of this discussion is herewith presented. It is generally agreed that the nerve supply of the kidney is derived solely from the autonomic nervous system, and is both sympathetic and parasympathetic. Parasympathetic fibers from the vagus nerve pass to the kidney by way of the celiac and aortic plexuses. The function of the parasympathetic nerves is not understood. The sympathetic nerve supply is mainly from the celiac ganglion and aortic plexus. Preganglionic fibers are received from the sixth thoracic through the first lumbar sympathetic ganglia, by way of the greater, lesser and least splenic nerves. A fine network of post ganglionic fibers surround the renal artery and its branches. Fibers also travel within the muscular

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Read at annual meeting, South Central Section of American Urological Association, Kansas City, Mo. September 21–23, 1953.

coat of the blood vessels. It is therefore evident that denervation of the renal vessels cannot be completely effective. Sympathetic nerves terminate within the smooth muscle tissue of the renal tubules and calyces. There are both efferent and afferent fibers. The efferent fibers are thought to cause constriction of the muscle cells and also vasodilation. Painful sensations arising in the kidney and ureter pass over the afferent nerve. The preganglionic fibers of the sympathetic system pass in the intermediolateral columns of the cord. There is evidence that there is cortical representation in the autonomic system in the premotor cortex of the frontal lobes. Following prefrontal lobotomy in the treatment of severe nervous disease, many disagreeable effects of a disturbed autonomic system have been relieved or ameliorated. It has therefore been suggested that patients suffering from nephralgia who have been classified as emotionally unstable, may have emotional instability which relieves itself by an overflow into the autonomic nervous system rather than by personal adjustment.

Maier, Engelmann, Wharton and others believe that the ureters can function automatically and initiate their own muscular contraction without the necessity of external neural connection. Barringer, Wu and Quinby are agreed that adequate stimulus for ureteral peristalsis is diuresis. Lapides demonstrated that ureteral peristalsis will continue despite interference with nerve supply to the ureters. He therefore believes that the ureter is an autonomous organ and that the autonomic ganglion takes no part in maintaining ureteral contraction. Caldwell, Marks and Rowntree denervated the renal pedicles of a group of dogs upon which subsequent renal studies were done. There was no change in the excretion of dyes. Concentrative powers of the kidneys were temporarily diminished. This persisted in one dog for two months. After five months, the only evidence of change in function was increased diuresis.

In 1921, Papin and Ambard advocated renal sympathectomy for the relief of renal pain associated with small hydronephrosis. They reported relief in four of six patients. Function tests reveal no difference in the function of the kidney following operation. There was no change in the hydronephrosis. A nephropexy and renal decapsulation was done on these patients. Therefore it is difficult to evaluate the results.

In 1943, Elmer Hess discussed renal denervation and mentioned the fact that the operation had been advocated for the relief of reflex anuria, nonmechanical hydronephrosis, early tuberculosis, prevention of renal calculi, hypertension and nephralgia. There was no evidence that the operation had been helpful in any but the latter.

In 1948, Granville Crabtree reported 8 patients upon whom renal denervation had been done. There was complete relief in five. In one there was a complete failure. One patient was probably relieved for two years and another for three years. He called attention to the fact that most patients with unexplained renal pain were of a highly nervous temperment and that neurosis had been diagnosed in almost all instances.

Elwood Young and associates were of the opinion that patients in this group should include those with abdominal or back pain of proven renal or ureteral origin in whom no obvious causes can be found, including those cases of minimal hydronephrosis for which no organic explanation can be found. They state that it has been shown that an autonomic reflex arch exists which is similar to the somatic arch and it is felt that an inbalance of the autonomic nervous system is a common cause of renal pain without demonstrable organic changes. Young suggested that following a complete physical examination and urological study, certain tests should be carried out to determine whether or not renal denervation might be expected to be of benefit. First, the administration of Etamon, with the idea of blocking the autonomic nerves. Second, administration of a placebo in the place of Etamon. The patients getting relief from the placebo should be treated on a psychotic basis. Third, unilateral paravertebral splenic chain and dorsal lumbar sympathetic ganglion block from D9 to L2 during an attack of pain. The patient whose symptoms are relieved by a sympathetic block, either by the use of novacain or by the use of Etamon, should respond to adequate denervation. Young reported five patients, one cured by nephrectomy, one relieved by frequent ureteral dilatations, one apparently relieved by ureteral dilatations and sympathetic block, one cured by sympathectomy, and one partly relieved by Etamon, placebos, parasympathetic excision refused.

I present 4 patients, all of whom have had previous operations for the relief of renal pain. Two are relieved by sympathectomy and one by a cordotomy. These three patients were practically invalids because of discomfort and at the present time are carrying on their normal household or business duties. The fourth patient has been relieved of pain in the left renal and ureteral areas. Since the sympathectomy was done she has been operated upon because of a herniated disk. At present she complains of pain in the right lumbar area. This pain is not constant, but quite severe at times. Because of the diagnosis of herniated disk shortly following the sympathectomy, the advisability of the operation has been questioned. The patient however is positive that she obtained definite relief from the sympathectomy. The operation in this case is not recorded as a complete success.

CASE REPORTS

Mrs. A. B., aged 34, was admitted to St. Elizabeth's Hospital November 30, 1950 because of pain in the right costovertebral area and in the lower part of her abdomen. The pain was of 6 years' duration but had gradually grown worse until she was practically incapacitated. In 1947 her right kidney was suspended without appreciable relief. Examination showed her kidney to be in good position. There was a slight angulation of the right ureter near the renal pelvis. The only other evidence of a pathological process was spasticity of the colon. She was treated 3 months with bed rest, ureteral dilatations, antispasmodics and placebos without improvement. March 14, 1951, a thoracolumbar sympathectomy was done and because of the angulation of the right ureter the kidney was exposed and freed of adhesions. An aberrant blood vessel at the lower pole was ligated and divided and all nerve trunks that could be identified were stripped from the renal artery. The kidney was fixed in a normal position.

Convalescence was uneventful. Twelve months following the sympathectomy she reported that she was in better health than she had been for several years and had required no medical attention since leaving the hospital.

Miss E. H., aged 33, was admitted to St. Elizabeth's Hospital November 18, 1950 because of pain in the left costovertebral area, radiating into the lower abdomen and left leg. She stated that she had had pain in her back or abdomen almost constantly since she was a child. Her history disclosed numerous hospital admissions. Her appendix was removed when she was 17 years old. A year later a partial excision of the right ovary and a presacral nerve resection was done. At that time a diagnosis of right ureteral stricture was made. Three years later, her right kidney was removed because of hydronephrosis and stone. Six years later, she had a left nephrolithotomy and at the age of 31, a cholecystectomy. Examination showed a poorly nourished but well developed young woman complaining of constant left costovertebral pain which varied in intensity. The pain frequently radiated into the lower abdomen and left leg. There was good function from the remaining kidney. There was no evidence of ureteral obstruction nor was there any dilatation of the renal pelvis. A small stone occupied the terminal portion of an upper calyx. After considerable deliberation, I decided to attempt denervation of the left kidney. The operation was extremely difficult. The kidney was larger than normal, densely adherent and could not be delivered into the wound without undue risk. The small stone could not be located. The capsule was stripped from the kidney and the wound closed.

She felt better for about a month, and then returned complaining of the same pain except more localized. She was then seen by two surgeons who after obtaining psychiatric consultation refused to do a lumbar sympathectomy. I was not convinced that the pain was on a psychoneurotic basis and advised that she consult a neurosurgeon in a near by city. He elected to do a cordotomy. Since this operation 2 years ago she has been employed regularly as a secretary and has not required medication for pain.

Mrs. B., a woman aged 35, was first seen August 4, 1952 because of pain in the left costovertebral area radiating to the lower abdomen. In August 1951 she had a right nephropexy and the left kidney had been suspended five months later. The patient stated that there had been no relief of pain on the left side following the operation. She gave a history of passing blood when the pain was severe. The urine contained blood in microscopic amounts. Her pain was to some extent relieved by Etamon but the side effects were such that she refused to take it.

After approximately 30 days' treatment with ureteral dilatations, antispasmodics and sedatives, a sympathectomy was done, removing the ganglia from the tenth dorsal to the first thoracic inclusive. The patient was not immediately relieved of pain but has gradually improved until at the present time there is no discomfort on the left side. One month following the operation she was again admitted to the hospital because of pain in the lower part of her back radiating into her left leg. In November she was operated upon for a protruded disk at the fourth interspace. This somewhat confuses the picture but it is doubtful that the herniated disk caused pain in the lumbar area. At the present time she has no left lumbar pain but has frequent attacks of pain on the right side of the abdomen.

Mrs. L. H., aged 41, was admitted to the Hospital Division of the Medical College of Virginia June 9, 1944 because of pain in the right lower quadrant of the abdomen and uterine bleeding. A perineal repair and a hysterectomy were done. Pathological diagnosis: myomas of the uterus. Inability to void required catheterization over a prolonged period. The patient had pyuria, chills and fever which gradually responded to ureteral catheter drainage. Because of persistent pain, an excretory urogram was made and showed moderate bilateral renal ptosis.

She was re admitted to the hospital 4 months later because of pyuria and pain in the left side of the abdomen. There was tenderness and general discomfort in both costovertebral areas. Both ureters were dilated to 12F. There was temporary relief of pain but during the next three years she had repeated cystoscopic treatments and was given every available antispasmodic and pain relieving drug.

Four years following her first admission, because of persistent bilateral flank pain exaggerated upon exertion and pyelectasis, bilateral nephropexy was done. Following this procedure she was entirely relieved of pain for 2 years.

April 1, 1951, twenty-eight months following nephropexy, she was again admitted to the hospital because of pain in the right flank and right lower quadrant of the abdomen. During the summer the right ureter was dilated several times and the patient required medication for pain almost constantly. At no time had there been any return of pain on the left side. November 11, 1951 she was again admitted to the hospital and a sympathectomy was done on the right side, removing the sympathetic chain and ganglia from D10 to L2. Also the greater and lesser splanchnic nerves from the D10 level to the celiac ganglion were removed. There was moderate discomfort in the right lumbar area and abdomen for three or four weeks after which she expressed herself as feeling quite well. She has not required medical attention since the sympathectomy was done.

Pain of renal and ureteral origin is not unusual without objective evidence of renal and ureteral disease. Such pain is probably caused by some disturbance of sympathetic nerve supply. The condition is usually spoken of as nephralgia. After thorough investigation has failed to discover a pathologic process to account for the pain, a correct diagnosis can usually be made by blocking the nerve supply to the kidney with novacain or by the administration of Etamon to produce an autonomic blockade. In many of these patients there is a decided psychic element which must be taken into account but the psychiatrist alone is rarely, if ever, successful in relieving the pain. Division of the autonomic nerve supply to the kidney either by renal pedicle denervation or by lumbar sympathectomy does not endanger the functional capacity of the kidney.

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PATHOGENESIS OF RENAL FAILURE

JOHN T. MACLEAN

We are concerned primarily with the mode of development of the lesion in the kidney which leads to the production of acute renal failure. It is presumed that the pre-renal causes of failure such as a diminished fluid intake, a reduction in the constituents of the blood as occurs in haemorrhage, diarrhoea and vomiting have been excluded. Likewise it is presumed that the post-renal factors which cause obstruction to the outflow of urine have also been excluded.

This process of elimination narrows our problem down to the specific problem of what is occurring in the intrinsic renal lesion, and what are the contributing factors in its production. Figure 1 represents a diagrammatic concept of the various contributing factors which will be discussed in more detail subsequently.

A. GLOMERULONEPHRITIS

Figure 2 shows a normal glomerulus. It is not difficult to visualize that in an acute inflammatory reaction the polymorphs rush to the scene of action, so that very soon the entire glomerulus becomes a seething congested mass of inflammatory cells (fig. 3). In addition, Bowman's capsule becomes filled with an inflammatory exudate. Likewise, it is not difficult to conceive that if a sufficient number of units are so involved and their function eliminated, that acute renal failure may ensue. Clinically, we are well able to recognize this type of lesion with the sudden onset of mahogany coloured urine, hypertension, marked albuminuria, many red blood cells and white blood cells in the urine, and granular casts, followed in a few days, in some cases, by anuria.

Sulfonamide anuria. Sulfonamide anuria should be mentioned and excluded. Its mode of onset may vary considerably. There are four types of lesion possible: 1) Seventy-five per cent are due to mechanical blockage of the ureters by mixed blood clot and crystals. We have had 3 cases of sulfonamide anuria admitted within the past month. All three were due to sulfamerazine. All three had mechanical obstruction of the ureters with blood clot and crystals. All three promptly recovered when the ureters were catheterized and the pelves washed out. The lesion may be 2) toxic glomerulonephritis, 3) focal necrosis, or 4) a lower nephron-nephrosis type of lesion with disruption of the tubule at several points along its course.

Bilateral diffuse cortical necrosis should also be excluded. This lesion is defined by Duff and Moore as a pathological entity of unknown cause manifested by extensive uniform necrosis of the cortex of both kidneys. There are two theories of origin: 1) that it is due to toxins, as in pregnancy; 2) that it is due to ischaemia causing vascular occlusions. Clinically there is oliguria, anuria, and pain, usually epigastric, radiating along the ureters. Edema of the dependent parts occurs. The outcome is usually fatal; however, a very few patients do recover.

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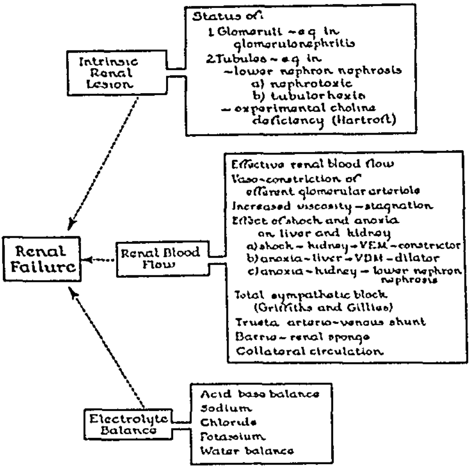

Status of
1 Glomeruli – e q in glomerulonephritis
2 Tubules – e q in
– lower nephron nephrosis
a) nephrotoxic
b) tubulorhexis
– experimental choline deficiency (Hartroft)
Intrinsic Renal Lesion
Effective renal blood flow
Vaso-constriction of efferent glomerular arteriole
Increased viscosity – stagnation
Effect of shock and anoxia on liver and kidney
a) shock – kidney → VEM – constrictor
b) anoxia – liver → VDM – dilator
c) anoxia – kidney – lower nephron nephrosis
Total sympathetic block (Griffiths and Gillies)
Trueta arterio-venous shunt
Barrie – renal sponge
Collateral circulation
Renal Failure
Renal Blood Flow
Electrolyte Balance
Acid base balance
Sodium
Chloride
Potassium
Water balance

FIG. 1. Diagram indicating main contributing factors in production of anuria

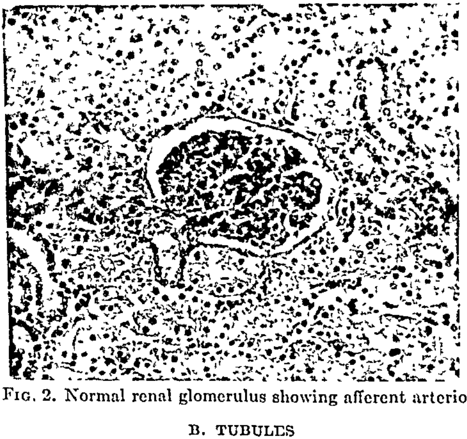


FIG. 2. Normal renal glomerulus showing afferent arteriole

B. TUBULES

A considerable amount of interest has centered around the lesion in the tubules. The exact sequence of events leading up to the production of "lower nephron nephrosis" still remains a matter of conjecture.

Lucké in 1946 gave an excellent description of the microscopic lesion, as being one of edema of the cells lining the distal convoluted tubules, followed by degeneration and necrosis of these cells. Numerous haem casts are also present. These are made up of myohaemoglobin and haemoglobin. There are two views held regarding the appearance of haem casts in the tubules. One is that haemo-

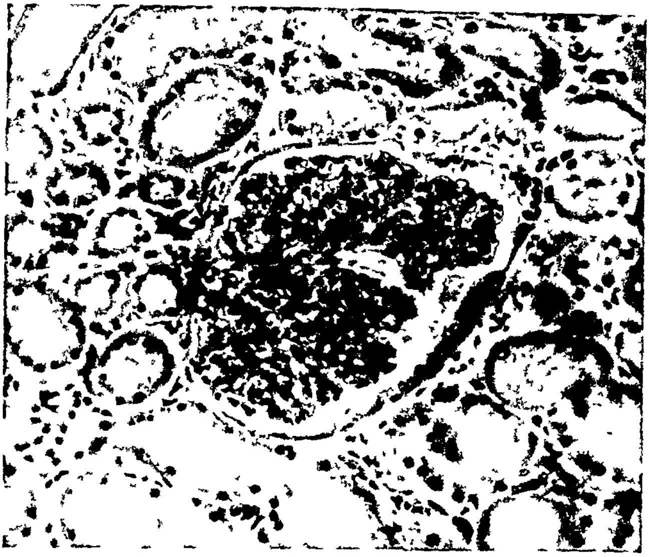


FIG. 3. Renal glomerulus in acute glomerulonephritis. Note inflammatory cells in glomerular tuft and protein exudate in Bowman's capsule.

globin may dissociate into molecules of smaller size and pass through the glomerulus, whereas myohaemoglobin is allowed to pass because of the increased permeability of the glomerulus. The other view is that these two compounds settle out in situ, from the debris locally present.

Much of the current work on this problem is divided into two phases: a) original investigation; b) a determined effort to eradicate the name and substitute another which renders the concept of pathogenesis even more opaque.

There are many names in medicine that are in their true sense misnomers, and yet have survived the years. The main objection to the name "lower nephron nephrosis" is that the lesion is not limited to the lower nephron, and that it is not a nephrosis but a nephritis. These seem like legitimate objections. However, if one concedes all this, it would still appear to be a reasonably good name.

Oliver et al. in 1951 reported on his investigations following the study of cases in which the individual nephrons were dissected out and studied. He believes that there are two types of lesion which may occur: A) Nephrotoxic damage. This occurs for example in mercury poisoning. The lesion is present only in the proximal convolutions, and is evenly distributed amongst all the nephrons. Debris may be packed within the lumen of the tubule, but the basement membrane remains intact. At the commencement there is a hydrops of the tubular cells followed by flattening of the epithelial cells, and death of the cells.

b) Tubulorhexis. Here there is disintegration of the tubular membrane, the epithelial cells become necrotic. This may involve only a portion of the wall of a tubule, or the whole wall may be involved resulting in loss of continuity. The lumen of the tubule thus lies open to the surrounding interstitial tissue. The interstitial reaction may be nil or it may be extreme. There may be masses of connective tissue fibres surrounding the tubule, or the surrounding reaction may be granulation tissue. This type of lesion is found in every segment of the nephron, but is most common in the terminal portion of the proximal convolution where it dips into the medulla, and in the distal convolution and connecting tubule.

What occurs next? In the portion of the tubule involved with the nephrotoxic edema and death of the cells, regeneration of the cells occurs, but function is not necessarily restored. In the tubulorhexis type of lesion, if there is some continuity of the tubule, regeneration may occur; whereas if the tubule is completely divided, it may never unite, or the ends may be invaded and obstructed by growing granulation tissue extending from the interstitial tissue.

One may reasonably question the isolationism of this theory of nephrotoxic damage. It is assumed that most toxins are more concentrated in the proximal tubule than elsewhere, and that the lesions they produce should be most intense in this region, and be continuous rather than segmental. Microscopically this is what actually does occur. On the other hand, it is rather difficult to imagine that a toxic substance in solution should suddenly loose its toxicity once it has passed a given point of the tubule. Oliver et al. state that more distal portions of the tubule do show tubulorhexis or disintegration of the tubular membrane, although in the crush syndrome the nephrotoxic lesion in the upper nephron is completely lacking.

In tubulorhexis when there is disintegration of the continuity of the tubular membrane, it is not surprising that there should be an interstitial tissue reaction. This is exactly what one would expect, and is precisely the same as what happens when the interstitial tissue is invaded by any other process such as occurs in pyelonephritis. In the latter, the response is inflammatory in nature.

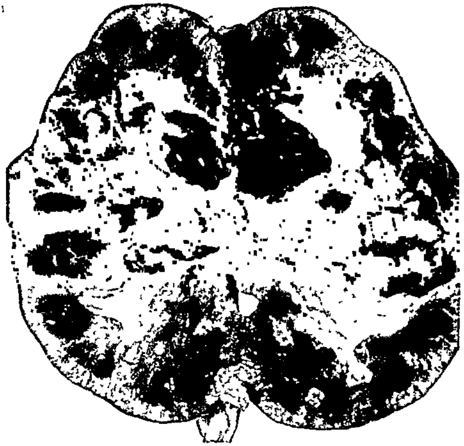


Fig. 4. Case No. 48-13883. Gross appearance of kidney in patient who died after partial recovery from acute renal failure Anuria developed following a 12 hour period of hypotension postoperatively Urinary output returned on the sixth postoperative day. Death occurred following evisceration of wound on sixteenth postoperative day.

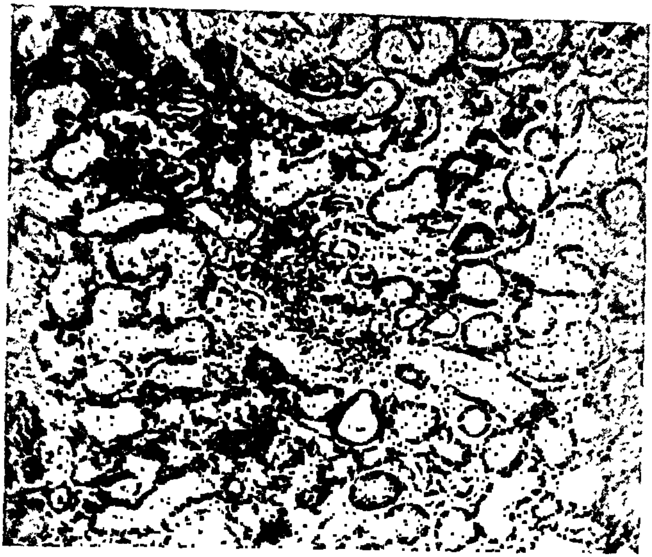


FIG. 5. Same case as figure 4. Microscopic section showing marked interstitial edema. Is it this edema which is choking off blood supply?

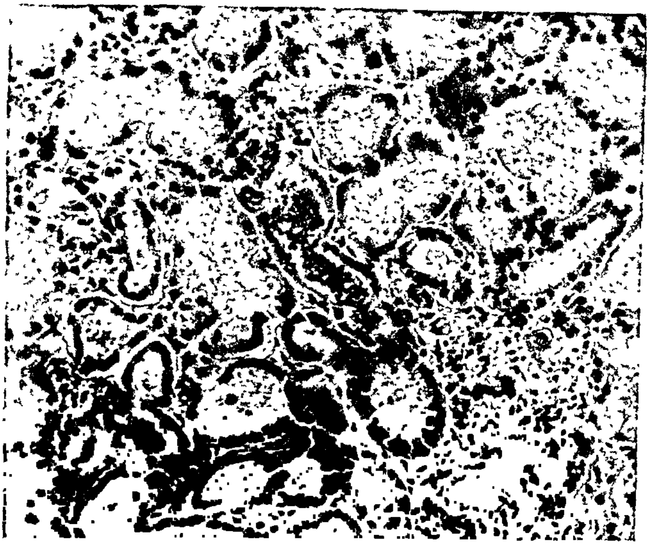


FIG. 6. Same case as figures 4 and 5. Microscopic section of another area showing haem pigment cast in tubule.

Figures 4, 5, 6, 7, and 8, from the author's cases, show some of the lesions described.

RENAL LESIONS IN EXPERIMENTAL CHOLINE DEFICIENCY

Hartroft has produced the "haemorrhagic renal syndrome" in experimental choline deficiency in weanlings and adult rats, and has described the pathogenesis. The initial lesion consists of the intracellular formation of sudanophilic droplets in the proximal convoluted tubules. He believes that the rapid appearance of the droplets may be responsible for the associated tubular swelling. This in turn causes pressure on the capillaries supplying the tubules, with resultant ischaemia and eventual necrosis of the tubules.

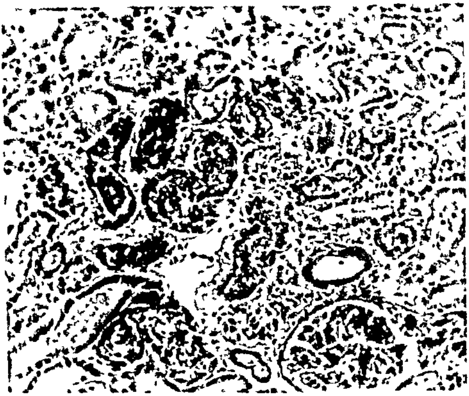


Fig 7. A-14194, case of retroplacental haemorrhage with death in uremia. Section shows casts in tubules with marked edema and infiltration around tubule. Tubule in lower left hand corner is disrupted (tubulorhexis).

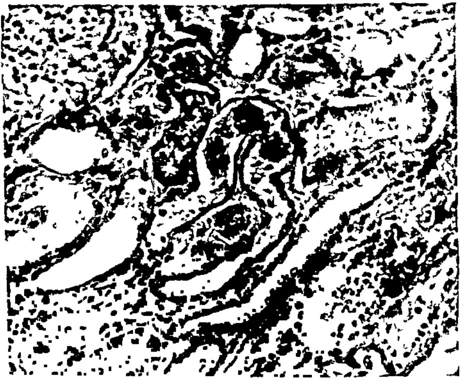


Fig 8. A-14284, case of post-transfusion anuria Section shows haem cast in tubule. Note that it is focal lesion, and that tubule both before it and after it is normal.

There would appear to be an extraordinary similarity between this type of lesion, and the nephrotoxic lesion described by Oliver et al.

In seeking a common denominator to explain the changes found in lower nephron nephrosis we must consider still other possibilities which might contribute to the production of this lesion. Referring back to figure 1, these are: the effects of:

1) Effective renal blood flow
2) Vasoconstriction of the efferent glomerular arterioles
3) Increased viscosity of the blood plasma, and stagnation

4) The effect of shock and anoxia on the liver and kidney
    a) Shock—Kidney produces V.E.M.—Vasoconstrictor
    b) Anoxia—Liver produces V.D.M.—Vasodilator
    c) Anoxia of kidney produces lower nephron nephrosis
5) Total sympathetic block
6) Trueta arteriovenous shunt
7) Barrie—Renal sponge
8) Collateral circulation

1) *Effective renal blood flow.* In man, 95 to 97 per cent of hippuran or diodrast added to human blood can be recovered from the plasma within 3 minutes. If for example 700 mg. of diodrast is excreted by the kidney in 1 minute, and the blood plasma has a content of 1 mg., it follows that 700 cc of plasma must have passed through the kidney in that period. This in turn represents a blood flow of 1300 cc per minute which is the normal effective renal blood flow in man for both kidneys.

It is possible to cannulate the renal vein and thereby measure the absolute renal blood flow. In some instances although the actual or absolute renal blood flow may remain unchanged, the effective renal blood flow may be considerably reduced as determined by para amino hippuric clearance tests.

Maluf, using India ink injections, has demonstrated in dogs that during the anuria or oliguria which follows the infusion of lysed red cells superimposed on reversible shock or dehydration, the cortex and medulla are equally injected with the dye, indicating a normal absolute blood flow, but there is a marked fall in the effective renal blood flow (as measured by renal clearance of para-amino hippurate), due to the inability of the obstructed tubule to allow the passage of hippurate.

This was also well shown in one of the cases described in detail by Oliver et al. The patient was admitted to the hospital following the ingestion of anti-freeze mixture. The amount taken was unknown. He was admitted complaining of bilateral renal pain and dyspnea. Red blood cells and albumin were found in the urine. On the twelfth day the urine excretion was 0.2 cc per minute. The blood urea nitrogen was 266 mg. per cent and the para-amino hippurate and inulin extractions were zero.

The effective renal blood flow is lowered a) when the blood pressure is lowered, as in shock; b) when the blood volume is lowered as in haemorrhage, or marked dehydration; c) in crush and the lower nephron nephrosis type of lesion.

2) *Vasoconstriction of the efferent glomerular arteriole.* Some workers believe that the lesion in lower nephron nephrosis is initiated by a vasoconstricton of the efferent arteriole leaving the glomerulus. This in turn causes a stagnation of blood leaving the glomerulus, and is progressive in a retrograde manner to the glomerular tuft. Since the blood supply to the tubular portions of the individual nephrons is derived almost exclusively from the vascular network formed from the efferent glomerular arteriole, it follows that if vasoconstriction occurs, there results an ischaemia, which in turn produces anoxia of the tubules, leading to their degeneration.

3) *Increased blood viscosity leading to stagnation.* It is recognized that in uremia there is an increased vicosity of the blood plasma. This in turn may increase any stagnation already present in the renal circulation.

4) *The effect of shock and anoxia on the liver and kidney.* Shock is a clinical syndrome which is the result of a malproportion between the circulating blood volume and the volume of the vascular capacity, leading to metabolic changes which may be reversible or irreversible. If the blood pressure and blood volume fall, anoxia of the tissue occurs.

In reversible shock, the organism attempts to compensate for this constriction of the blood vessels of the skin, spleen, etc. to make blood available for the heart. During the anoxic period, the kidney produces a vasotropic substance V.E.M. which causes constriction of the arterioles. This in turn tends to maintain the blood pressure by diverting the blood from the periphery, and making it available to the essential organs, thus leading to recovery from the shock.

Anoxemia of liver: If, however, the stage of shock is continued beyond a certain period, the process becomes irreversible. The continued anoxemia exerts its effect upon the liver resulting in an altered metabolism, and the production of a vasodilator substance V.D.M. This substance has the opposite effect to V.E.M., and causes dilatation of all the arterioles of the body, resulting in pooling of the blood in the capillaries and arterioles.

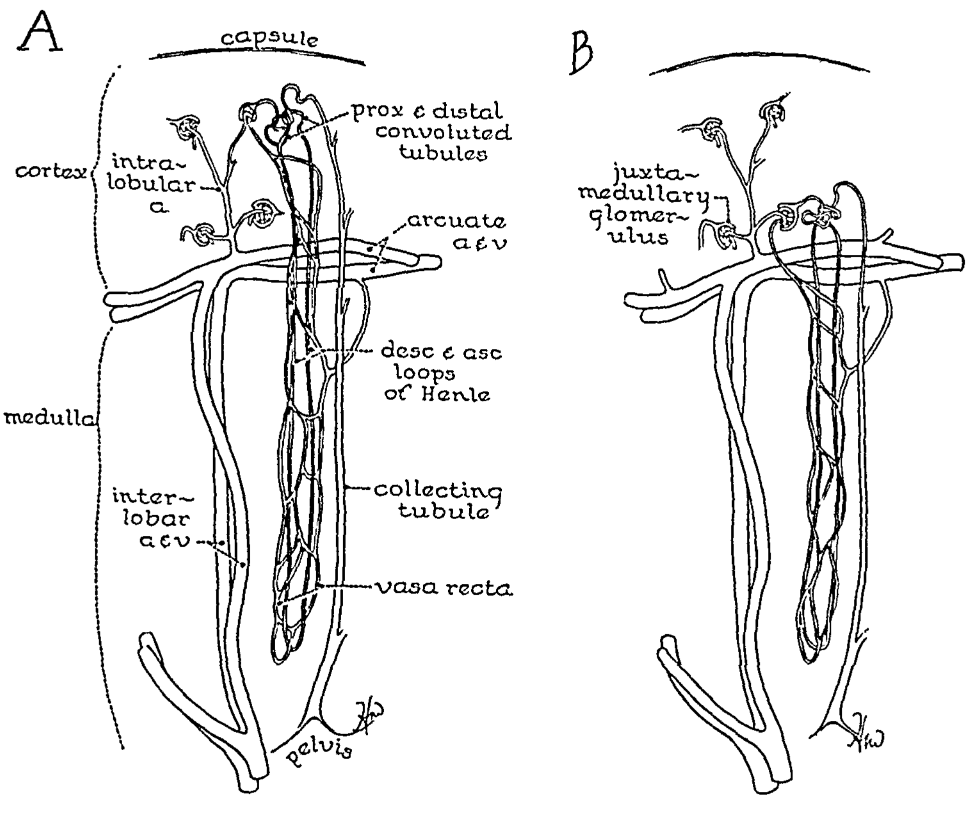
Anoxia of kidney: Glomerular filtration depends on the blood flow through the kidney, and blood pressure. In shock there is decrease in the blood flow through the kidney at a diminiished rate, and consequently there is a diminished volume of filtrate produced. This small amount of urine is reabsorbed by the tubules so that oliguria occurs, giving a urine with a high specific gravity. The tubules are as yet unaffected. The nonprotein nitrogen rises, but this is due to failure of filtration i.e., extrarenal uremia.

However, if the anoxia is maintained the tubules themselves become damaged and a true lower nephron nephrosis develops. The normal structure is lost and the normal functions of water absorption and selective reabsorption of waste products are also lost. The urine may now flow directly from the tubule into the blood. Haemoglobin casts will be found in the tubules. As the lower nephron nephrosis develops, it becomes a true renal uremia.

When liver damage due to anoxia occurs with renal failure, the condition is called "the hepato-renal syndrome."

5) *Total sympathetic block.* Griffiths and Gillies of Edinburgh working on "Total Sympathetic Block" have produced impressive observations, some of which are entirely contrary to what we have always believed.

In the cases reported, they intentionally produced a total sympathetic block so the surgeon could perform a thoraco-lumbar splanchnicectomy and sympathectomy. Premedication consisted of omnopon and hyoscine. In the anesthetic room, thiopentone was given intravenously, usually 1 gram. A lumbar puncture is done in the second lumbar space, and 150 to 250 mg. of procaine dissolved in 3 to 4 cc of cerebrospinal fluid injected. The patient is turned on his back and placed in sharp Trendelenberg position. This position is maintained until the



Normal

Trueta Shunt

FIG. 9. Indicating normal renal circulation, and diversion through "Trueta-shunt"

blood pressure starts to fall. An airway is inserted, and 100 per cent oxygen administered. The patient is then postured in the lateral "jack-knife" position. The blood pressure drops off to zero and stays unrecordable throughout the operation. The brachial and radial pulses are not palpable. The anesthesia is believed to extend up to and involve the first thoracic area, although this cannot be accurately determined as the patient is given thiopentone intravenously prior to the lumbar puncture.

In most cases an almost ischemic operative field is obtained. They report 84 operations involving 44 patients with only one death. (This patient had a pleural effusion on the opposite side.)

The interesting feature is that they regard the hypotension as perfectly harmless. Clinically, it has always been accepted that a minimal systolic pressure required to maintain effective filtration pressure was 75 mm Hg. They state, "At pressures lower than this, secretion of urine is much diminished and may even cease, but while effective ventilation with oxygen is maintained as in the technique described, viability of the renal epithelium is not endangered; when the systolic pressure rises to the level necessary for filtration, secretion of urine starts". In this series 3 patients showed a reduction in the output of urine during the first 36 hours after operation."

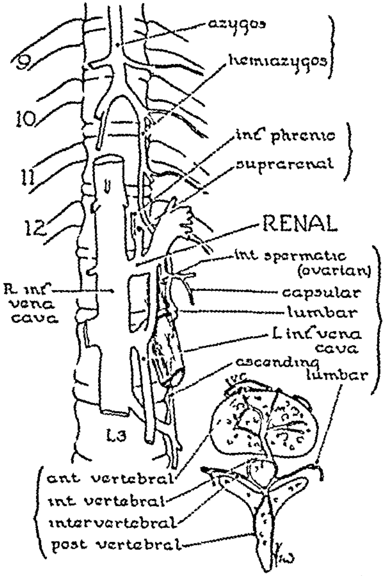


Fig 10 Showing collateral circulation of kidney Note that left renal vein is situated at center of a collection of venous channels 1) inferior phrenic and suprarenal tributaries from above, 2) communications with azygos and hemiazygos vein, 3) communications with set of internal and external vertebral plexuses via intervertebral and lumbar veins (Modified after Anson Surg, Gynec & Obst, 84 : 6, 1947)

The oxygen consumption of the normal and diseased human kidney has been studied by Cargill and Hickman, and by Clark and Barker

6) *Trueta arteriovenous shunt (juxtamedullary glomeruli)* Trueta and his associates have described two types of glomeruli designated cortical and juxtamedullary The juxtamedullary glomeruli are larger than the cortical The term cortical glomerulus is used to denote a glomerulus whose efferent vessel is of small caliber and which breaks up to form part of the cortical intertubular capillary network The term 'juxtamedullary glomerulus' is used to denote a glomerulus whose efferent vessel is of large caliber and which passes into the medulla to divide into vasa recti (fig 9) These workers believe that the kidney has two potential circulations, a greater and lesser Under extreme conditions, the blood may pass almost exclusively through one or the other Experimentally this may be true Clinically, there is no evidence in man that such a shunt does occur

7) *Barrie arteriovenous shunt* Barrie's work on the renal sponge would indicate that the renal medulla may have a blood supply independent of the glomerular circulation However, the conditions which Barrie described are found only in abnormal kidneys, and are probably not a normal structure Their relationship to acute renal failure has as yet not been clearly defined

8) *Collateral circulation* In certain cases of renal failure due to mechanical ob-

struction of the inferior vena cava, the collateral circulation of the kidney may be of paramount importance. The anatomy of the pararenal system of veins has been well described by Anson et al. (fig. 10).

On the right side the suprarenal vein and gonadal vein each empties separately into the inferior vena cava.

On the left side, the left renal vein is found to be situated at the center of a collection of venous channels: 1) the inferior phrenic and suprarenal tributaries from above; 2) communications with azygos and hemiazoygos vein; 3) communications with the set of internal and external vertebral plexuses via intervertebral and lumbar veins.

SUMMARY

In seeking a common denominator which would apply to the various factors discussed above, as contributing in the production of acute renal failure due to an intrinsic renal lesion, anoxia of the kidney or part of the kidney would appear to offer the most likely explanation.

The work of Selye on the General Adaptation Syndrome, and the possible effect of ACTH on the pathogenesis of acute renal failure have not been discussed. Although the theories behind this have considerable appeal, it is impossible to draw any conclusions at the present time.

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RENAL FUNCTION STUDIES IN POLYCYSTIC DISEASE OF THE KIDNEY: A PRELIMINARY REPORT

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Little information is available regarding discrete renal function studies in polycystic kidney disease It is the purpose of this communication to report certain preliminary results obtained in the study of renal functions and electrolyte excretion in patients with this disease, evaluated prior to and following surgical decompression of the kidneys The data include pre- and postoperative measurements of glomerular filtration rate (GFR), effective renal plasma flow (ERPF), maximum tubular secretion of p-aminohippurate (Tm_{PAH}), and renal excretion of sodium, chloride and potassium

CASE MATERIAL

The present studies were performed on two adult male patients, both on active military duty at the time of diagnosis The diagnosis of polycystic renal disease was based upon standard criteria, including dull persistent flank pain, bilateral palpable abdominal masses, and characteristic x-ray patterns following intravenous and retrograde urography. Case 1 (aged 40) was untreated prior to entrance into the hospital (fig 1, *A*) Case 2 (aged 30) had been exposed to a surgical procedure for decompression of one kidney four months before the time of the present studies (fig 1, *B*) Control data on case 1, therefore, precede surgical decompression of either kidney, whereas control data on case 2 precede decompression of the unoperated kidney Postoperative studies were performed 5 weeks following surgery in case 1 and 6 weeks following surgery in case 2

Surgical exposure of the kidney was performed through the usual lumbar approach The operated kidneys were fully exposed and decompression was effected as completely as possible by excision of the larger cysts, destruction of the smaller cysts by multiple linear incisions through the cortex and aspiration of the deep cysts An attempt was made to preserve normal parenchyma Photographs of the kidneys before and after decompression are reproduced in figures 2 and 3

METHODS

The pre- and postoperative studies were performed in the morning with the patients in the fasting state One liter of water was administered 60–90 minutes before studies were begun Additional water in 200 cc amounts was offered twice during the course of each series of clearance measurements in order to maintain urine flows in excess of 2 cc per minute

Venous blood samples were drawn through an inlying 17-gauge thin-walled needle into heparinized syringes and discharged into heparinized tubes A total of 0 1 cc of heparin was used per 10 cc of blood Following each sampling of blood, 0 3 cc of a dilute (1 10) solution of heparin was instilled into the needle and the needle closed with a Luer-plug Because no difficulty with clotting was experi-

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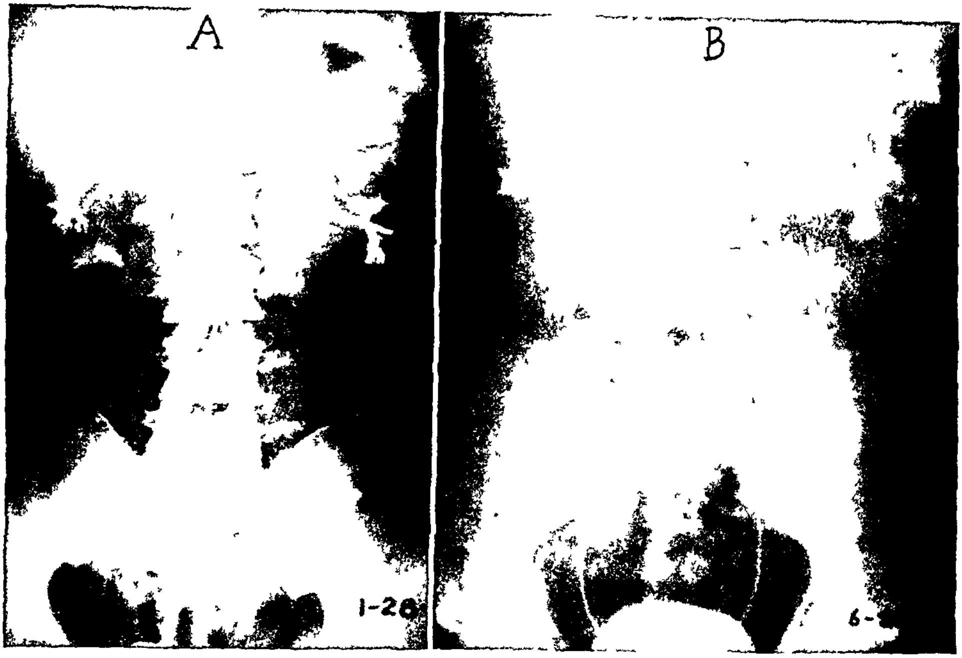

FIG. 1. *A*, retrograde pyelograms in case 1 prior to surgery. *B*, retrograde pyelograms in case 2 prior to surgery.

enced in runs up to five hours in duration, this method was preferred to the use of polyethylene catheters which frequently necessitated venous exposures. To prevent dilution from the heparin in the needle, a 2 cc blood sample was aspirated (in a separate syringe), and discarded prior to each sampling.

The bladder was catheterized with a multi-eyed rubber catheter. Two minutes before the completion of each urine collection period, bladder-washing was initiated. Two successive 10 cc aliquots of sterile distilled water were used, followed by two or more instillations of air. The latter was accompanied by suprapubic pressure. The total washout period was designed to last 2 minutes.

A timed urine sample and a blood sample were collected prior to administration of inulin and PAH primes for determination of inulin and PAH blanks. Prime injections were calculated to yield a plasma inulin concentration of approximately 30 mg. per cent and a PAH concentration of 2–3 mg. per cent.*

Sustaining infusions were administered in a normal saline vehicle through rubber tubing into the "inflow arm" using a constant infusion pump.† Sustaining solution A (inulin-clearance: C_{in}; and PAH clearance: C_{PAH}) was delivered at 1.5 cc per minute. Sustaining solution B (C_{in} and Tm_{PAH}) was delivered at 3.0 cc per minute. Rates of flow were calibrated at 15–30 minute intervals and were found to vary less than one per cent from the predicted rate.

Following administration of the priming injections and the start of sustaining solution A, a period of 30–40 minutes was allowed for equilibration of plasma

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* Inulin was obtained as 10 per cent solution from William R. Warner; PAH as sodium para-amino-hippurate in 20 per cent solution from Sharpe and Dohme; Heparin as heparin sodium injection from Lederle Laboratories.

† Bowman Infusion Pump Model 2: Process Instruments Co., 60 Greenpoint Ave., Brooklyn, 22, N. Y.

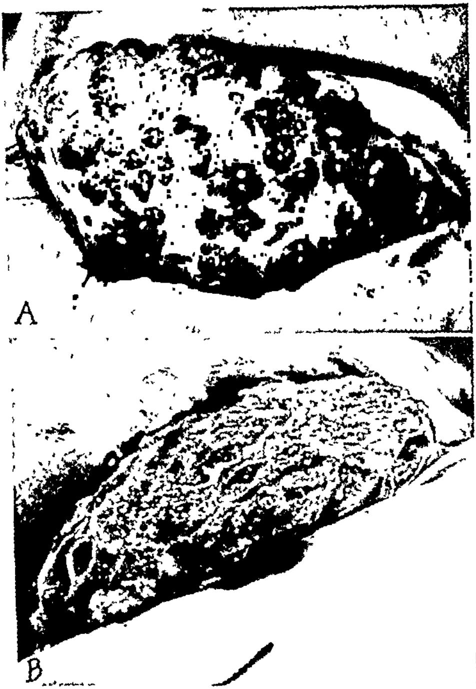

FIG. 2. Photographs of exposed kidney in case 1, before and after surgical decompression.

concentrations of inulin and PAH. Three to four 15–20 minute clearance periods were employed for determination of C_{in} and C_{PAH}. Priming for Tm_{PAH} measurements was accomplished by the administration of 60–70 cc of PAH through a three-way stopcock in the infusion tube at the rate of 10 cc per minute. A second period of equilibration was allowed and three 15–20 minute periods were employed for measurement in C_{in} and Tm_{PAH}. Blood was collected at the midpoint of each period and centrifuged immediately. Plasma was separated for analysis of inulin, PAH, Na, K, and Cl. Inulin was determined according to a modification of the method of Roe et al.[1] PAH was determined according to the method of Smith et al.[2] Chloride was determined according to the method of Van Slyke and Hiller.[3] Na and K were determined on a Baird internally compensated flame photometer.

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[3] Van Slyke, D. D. and Hiller, A.: Application of Sendroy's iodometric chloride titration to protein-containing fluids. J. Biol. Chem., 167: 107, 1947.

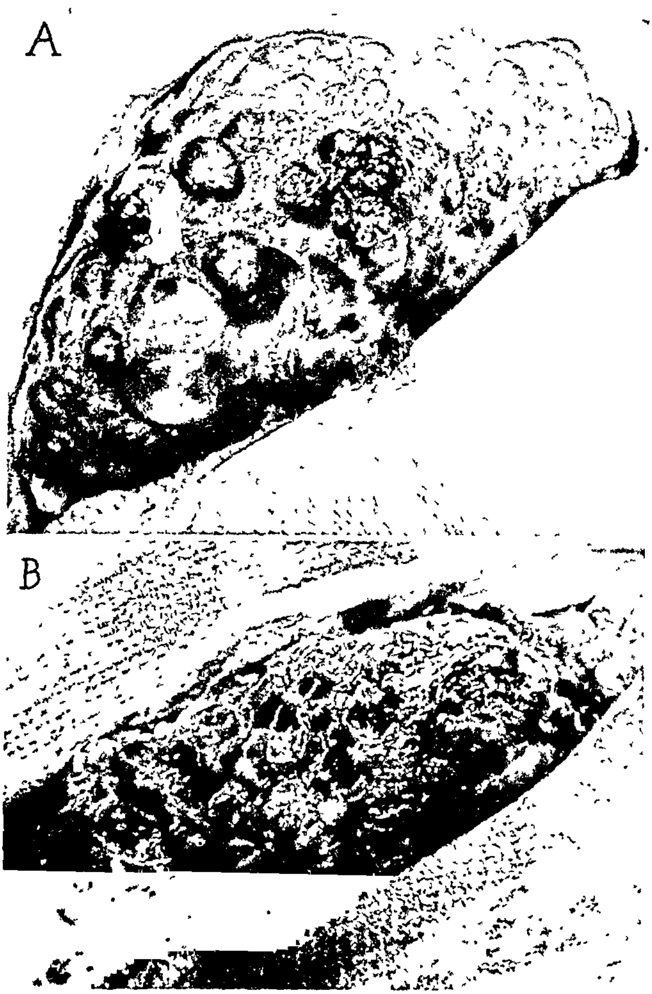

FIG. 3. Photographs of exposed kidney in case 2, before and after surgical decompression.

Plasma and urine inulin recoveries were run with each set of unknowns as a check on the degree of analytical accuracy. Recoveries averaged 100 per cent with extremes of 94 to 106 per cent. All inulin used was drawn from a single lot, which was found to be fructose free by yeasting aliquots prior to analysis by the resorcinol method.

Clearances were calculated by standard methods[4] without correction for delay time.

RESULTS

Average values for renal clearances are recorded in table 1.

Glomerular filtration rate. Low values for inulin clearance were obtained in both patients in control (i.e. preoperative) studies. The deviation from normal was more marked in the patient who had undergone previous decompression of one kidney (case 2), but, in this patient, the disease itself was more advanced.

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[4] Goldring, W., and Chasis, H.: Hypertension and Hypertensive Disease. New York: The Commonwealth Fund, 1944.

TABLE 1 *Renal function in polycystic disease of the kidneys Studies before and after surgical decompression of cysts*

	CASE I			CASE II		
	Preoperative	Post operative	% Change post op	Preoperative	Post operative	% Change post op
C_{in} (prior to PAH loading)	85.5	79.7	−6.8	66.8	45.8	−31.4
C_{PAH}	383	366	−4.4	288	196	−29.2
F F × 100	22.5	21.8		23.2	23.4	
TM_{PAH}	77.4	60.3	−22.1	42.7	39.2	−8.2

Values represent the average of three or more successive determinations

Definition of symbols

C_{in} = inulin clearance (cc/min)

C_{PAH} = PAH clearance (cc/min)

F F = filtration fraction $\left(\frac{C_{in}}{C_{PAH}}\right)$

TM_{PAH} = maximal tubular excretion PAH (mg/min)

C_{in} *values used in calculating F F were obtained prior to PAH loading*

All values are corrected to 1.73 sq m body surface area

Following surgical decompression a further decrease in filtration rate was noted *in both patients In case 1* the decrease in C_{in} was slight, in case 2 the decrease was more marked, amounting to 31.4 per cent of the preoperative value

Effective renal plasma flow Clearance of PAH tended to parallel C_{in} Both patients had control values considerably below normal Following surgery C_{PAH} declined slightly in case 1, and to a greater degree in case 2

Filtration fraction The ratio of $C_{in}:C_{PAH}$ was within the normal range[5] in both cases preoperatively Following surgery, filtration fractions remained essentially constant illustrating the parallel nature of the changes in C_{in} and C_{PAH}

Maximal tubular secretion of PAH The average preoperative value for Tm_{PAH} was normal in case 1 and depressed in case 2 Following surgery, Tm_{PAH} declined in both cases The greater decrease occurred in case 1, whereas C_{in} and C_{PAH} declined to a greater degree in case 2 In view of the known lability of Tm_{PAH} the magnitude of Tm changes cannot be interpreted at this time

Excretion of electrolytes Data on plasma concentrations and minute rates of excretion of Na, K, and Cl, together with computations of filtered load of Na and K are recorded in table 2 The figures for filtered load are uncorrected for plasma water content and the Donnan effect Computations of the per cent of filtered Na and K excreted ($C_{Na,K}$ C_{in}) are included to illustrate the change in electrolyte excretion following PAH loading in the postoperative as compared to the preoperative state The control values for this ratio are not intended to indicate the efficiency of tubular reabsorption of electrolytes

Sodium Plasma sodium values were within the normal range in all instances Following PAH loading, which imposes the necessity of excreting large amounts of anion, the excretion rate of Na increased abruptly in all experiments In both

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[5] Smith, H W The Kidney, Structure and Function in Health and Disease New York Oxford University Press, 1951

TABLE 2. *Renal excretion of electrolytes in polycystic disease of the kidneys before and after PAH loading (pre- and postoperative studies).*

PT.	STATUS	CONDITION OF EXPERIMENT	Cin cc/min.	Na				Cl		K			
				PNa mEq/cc	F.L. mEq/min.	E.R. mEq/min.	$\frac{CNa}{Cin} \times 100$	PCl mEq/cc	E.R. mEq/min.	PK mEq/cc	F.L. mEq/min.	E.R. mEq/min.	$\frac{CK}{Cin} \times 100$
1	Pre-op.	Control (2)	80.9	.146	11.8	.368	3.12	.111	.322	.0045	.366	.099	27.2
		PAH loading (2)	81.7	.147	12	.873	7.3	.109	.317	.0043	.352	.121	34.6
	Post-op.	Control (3)	79.7	.142	11.3	.249	2.3	.110	.209	.0038	.303	.075	24.63
		PAH loading (3)	67.8	.144	9.7	.60	6.2	.109	.161	.004	.271	.787	32.4
11	Pre-op.	Control (1)	84.2	.142	11.9	.498	4.2	.110	.426	.0045	.377	.094	24.9
		PAH loading (1)	97.4	.144	14.1	.767	5.5	.106	.331	.0038	.372	.079	21.2
	Post-op.	Control (4)	58.5	.144	8.35	.329	3.9	.109	.332	.0046	.269	.084	31
		PAH loading (3)	54.9	.147	8.08	.738	9.2	.108	.342	.0042	.232	.095	41.1

Number of determinations from which values are derived is indicated in parentheses.
Definition of symbols:
P_{NA}, P_{CL}, P_K = Plasma concentration of designated electrolyte;
F.L. = *Filtered load* (plasma *concentration* × C_{in}); E.R. = Excretion rate (urine *concentration* × minute urine flow); $C_{ELECTROLYTE}/C_{in} \times 100$ = per cent filtered load excreted; other *definitions* are included in Table 1.
Values for C_{in} are uncorrected for surface area.

cases, the ratio $\frac{C_{Na}:C_{in}(\text{Control})}{C_{Na}:C_{in}(\text{PAH load})}$ decreased following surgery. Although this is suggestive of a decreased ability of the tubules to retain Na postoperatively under the conditions of the experiment, alternate explanations are possible.

Potassium. Plasma K levels were consistently within the normal range. The *ratio of* $C_K:C_{in}$ *was above that found in the presence of a normal filtration rate,*[6] however the comments made above regarding this ratio appear to pertain to K as well as Na. The ratio $\frac{C_K:C_{in}(\textit{control})}{C_K:C_{in}(\text{PAH load})}$ decreased following surgery in both cases.

Chloride. Plasma chloride values were within the normal range in both cases in all studies. The effect of PAH loading upon the excretion rate of chloride was inconclusive.

DISCUSSION

There has been an increased interest in the surgical treatment of polycystic disease of the kidneys during the past decade as evidenced by the writings of Goldstein,[7] Cahill and Fish,[8] Dodson,[9] Rathbun,[10] Newman,[11] Howard[12] and others There is general agreement among these authors that in selected cases renal function is improved and life is prolonged by surgical intervention The mechanism by which this occurs is not clearly defined but the accepted explanation is that decompression of the kidney by rupture of the cysts results in release of untoward pressure on the remaining functioning nephrons

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[6] Earle, D. P., Farber, S. J., Alexander, J. D. and Pellegrino, E. D.: Renal function and electrolyte metabolism in acute glomerulonephritis. J. Clin. Invest., **30**: 421, 1951.

[7] Goldstein, A. E.: Polycystic renal disease with particular reference to author's surgical procedure. J. Urol., **66**: 163, 1951.

[8] Cahill, G. F. and Fish, G. W.: Surgical aspects of polycystic disease. Trans. Am. Assoc. G.-U. Surg., **34**: 81, 1941.

[9] Dodson, A. I.: Surgical treatment of polycystic disease of the kidney. J. Urol., **57**: 209, 1947.

[10] Rathbun, N. P.: Polycystic disease. Trans. Am. Assoc. G.-U. Surg., **35**: 131, 1942.

[11] Newman, H. R.: Congenital polycystic diseases. Am. J. Surg., **80**: 410, 1950.

[12] Howard, T. L.: Personal communication.

This present study cannot be considered as an assessment of the value of surgical treatment, since the follow up period is insufficient Temporary impairment of renal function is not infrequently observed following a variety of surgical procedures on the kidney, and when impairment already exists recovery from the surgical insult may be protracted Prolonged studies will be necessary to determine ultimate results

The possibility exists that the cystic nephrons may serve as functioning units In postmortem studies performed on two cases of polycystic disease, Lambert[13] was able to demonstrate inulin in the cyst fluid 15 and 96 hours after ante-mortem intraperitoneal inulin injection In studies performed in this laboratory[14] inulin has been administered intravenously to polycystic patients at the time of surgery and fluid has been aspirated directly from numerous cysts It has been found that inulin may appear in the cyst fluid within a matter of minutes in appreciable concentrations If the inulin entering the cysts can be attributed solely to glomerular filtration, the connection of the cysts to functional glomeruli appears likely * Further studies performed by Lambert[13] and by the present authors[14] have revealed a wide range of creatinine concentrations in fluid taken from different cysts in the same kidneys The presence of a gradient of creatinine concentrations suggests that the cysts may be intimately associated with functioning tubules, and the corollary exists that the more concentrated the creatinine the more distal the cyst lies along the course of the nephron Finally, postmortem reconstruction of cystic nephrons of polycystic kidneys by Lambert[13] and Norris and Herman[15] has revealed a glomerulo tubular continuity of cystic nephrons

This accumulation of data gives credence to the concept that the cysts are attached dynamically to functioning nephrons, and if this is true, the process of decompression of the kidneys by destruction of cysts may involve loss of multiple functioning units In light of this, it may be postulated that if the procedure is to improve function it must relieve compression of normal renal parenchyma sufficiently to compensate for this loss Further evaluation of these concepts is indicated

SUMMARY

Renal function and electrolyte excretion have been studied in 2 patients with polycystic renal disease before and after surgical decompression Function was depressed prior to surgery in both patients and further depression was noted 5 and 6 weeks following surgery

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* Studies are in progress to evaluate the possibility that some inulin may enter the cyst fluid by diffusion across the cyst wall

[13] Lambert, P P Polycystic disease of the kidney Arch Path , 44 34, 1947

[14] Bricker, N S , and Patton, J F Studies of the dynamics and chemical anatomy of cyst fluid in cystic disease of the kidneys (abstract) Clin Res Proc 2 22, 1954

[15] Norris, R F and Herman, L Pathogenesis of polycystic kidneys reconstruction of cystic elements in 4 cases J Urol , 46 147 1941

Plasma concentrations of Na, K, and Cl were within normal limits in all experiments. The excretion of Na and K relative to filtration rate was increased by PAH loading to a greater degree in the postoperative state than in the preoperative state.

The possibility that cystic nephrons contribute to renal function was discussed.

The authors give credit to Dr. C. A. Moyer who provided the stimulus for this study, and also acknowledge the invaluable assistance of Claude H. Schmidt, 1st Lt., M.S.C.; Ronald T. Caldwell, B.S., Pfc.; Doris C. Gomez, B.S.; and Melicent E. Hane, B.S.

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UPPER URINARY TRACT DISEASE ASSOCIATED WITH URETHRAL STRICTURE

J. DENNY MOFFETT, JR. and DAVID W. GODDARD

Stricture of the urethra in the male is a common disease and one that requires sustained treatment. In following the progress of numerous patients with urethral strictures it was observed by Beard and Goodyear[1] that co-existing disease of the upper urinary tract was seen with surprising frequency and usually as an incidental finding. Their observations stimulated our interest to investigate this subject further.

The association of upper tract disease with urethral stricture is mentioned in the textbooks, but the literature is scanty on the subject. A study of the literature reveals that Dourmashkin and Solomon[2] found the incidence of renal and ureteral calculi to be 22.6 per cent in their series of 84 men and women who had urethral obstruction. Birdsall[3] observed the frequency of hydronephrosis and renal calculi with obstructive lesions of the urethra.

With this in mind, a routine investigation of the upper urinary tracts of all patients with urethral strictures coming under observation over an 8 month period in the urological department of Grady Memorial Hospital in Atlanta was made. It is believed that the results of this study should be of interest.

This investigation was carried out on 152 consecutive patients with urethral stricture. Most of the strictures were sequellae of gonorrhea, the others were post-traumatic or postoperative. Twenty-seven patients were found to have additional obstruction to the lower urinary tract, these were excluded from this series. Those patients studied included 11 white and 114 Negroes. Ages of the patients ranged from 14 to 79, the majority being between 20 and 40 years of age. The strictures varied in severity from impassable to those well dilated.

In addition to pertinent history and examination of the urethra, routine investigation consisted of intravenous urography or retrograde pyelography or both, microscopic examination and culture of the urine, and blood chemistry studies of renal function.

Forty-seven of the 125 patients, or 37.6 per cent, were found to have one or more diseases of the upper urinary tract.

Twenty patients, or 16 per cent, were observed to have renal calculi. The calculi ranged from those barely recognizable to large, staghorn types. Eleven patients had a single stone, others had multiple stones. Bilateral calculi occurred in 3 patients. In conjunction, of those patients with stones, 8 had pyelonephritis, 5 had hydronephrosis, and 2 had hydro-ureter alone. Pyonephrosis occurred in 2 patients, both of whom had staghorn calculi.

Almost one fourth of the group demonstrated either hydronephrosis or hydro-ureter of varying degree.

Read at annual meeting, Southeastern Section of American Urological Association, Havana, Cuba, March 26–29, 1953.

[1] Beard, D. E. and Goodyear, W. E.: Urethral stricture. A pathological study. J. Urol., 59: 619–625, 1948.

[2] [illegible] lomon, A. A.: Upper urinary tract lithiasis. A frequent [illegible] J. Urol., 48: 196–203, 1942.

[3] [illegible] lesions of the urinary tract and their relationship in the production of renal pathology. Clinics, 3: 70–89, 1944.

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ANTIBIOTIC THERAPY OF URINARY TUBERCULOSIS: AN INTERVAL REPORT OF SIX YEARS EXPERIENCE

REED M. NESBIT AND CHARLES C. MACKINNEY

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Over six years have now elapsed since the advent of antibiotic therapy in genito-urinary tuberculosis. In a preliminary report[1] 2 years ago, the cases of 64 patients treated at the University of Michigan Hospital for tuberculosis of the urogenital tract were reviewed. The present communication is a follow-up study of this original group together with data on 26 additional patients treated since that time. The most recent cases have been observed for a minimum period of 6 months after the completion of antibiotic therapy.

INCIDENCE

Of the 90 patients treated in this series, 57 were males and 33 females. The age of the patients varied from 18 months to 72 years with over two-thirds being between the ages of 20 and 50 years. The presenting signs and symptoms are summarized in table 1.

Fifty-three of the patients had concurrent active tuberculosis apart from the genito-urinary tract or gave a history of it. Forty-four of the 57 male patients had positive clinical evidence of genital involvement.

MODE OF TREATMENT

During the first 2½ years of study the patients received streptomycin in doses of 1.0 to 2.0 gm. daily for periods varying from 40 to 120 days. Since that time dihydrostreptomycin has been given, using a basic regimen of 2.0 gm. daily for 90 days. Seventy-five per cent of the patients in this latter group received a total of 180 gm. dihydrostreptomycin in 90 days. Because of circumstances arising during therapy, the remainder received variations from this basic program. Antibiotics have been used to augment rather than supplant the well established principles used in combating tuberculosis, and for this reason sanatorium care during antibiotic therapy and for 6 to 12 months following medication has been considered essential. All cases in this series were studied by cystoscopy, retrograde pyelography and renal function tests; and 24 hour bladder urine as well as individual kidney specimens were tested by culture methods and guinea pig inoculation.

Para-amino salicylic acid has been used in treating our patients since the value of this substance has been recognized, but we have continued to employ daily 2.0 gm. doses of the antibiotic even though most investigators today advocate a smaller dosage given less often. There are certainly valid reasons for the latter regimens but their ultimate value has yet to be assessed. Many phthisiologists have urged us to continue with the regimen of large daily dosage so as to provide a basis for comparison of long term results with other plans of treatment, and

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Read at annual meeting, American Association of Genito-Urinary Surgeons, Hot Springs, Va. May 6-8, 1953.

[1] Nesbit, R. M., and Thirlby, R. L.: Results of streptomycin therapy in urinary tuberculosis; A four year review. J. Urol., 68: 394-398, 1952.

TABLE 1. *Presenting symptom or sign*

	CASES
Irritative bladder symptoms	40 patients
Epididymitis	17 patients
Hematuria	13 patients
Pyuria	13 patients
Flank pain	7 patients

since this series comprises a significant number of cases the policy would appear to be justified until some regimen had demonstrated a clearly defined superiority.

The present program then consists of complete rest in a sanatorium, dihydrostreptomycin 2 gm. daily, and PAS 12 to 15 gm. daily. Isoniazid is used as an addition to this regimen when a second course of therapy is used either for relapse cases or those which fail to respond to the initial 90 day course.

In unilateral renal disease, when small lesions are demonstrated in the pyelogram, antibiotic therapy is administered for 60 days then a check-up examination is made If substantial improvement has not occurred, nephrectomy is performed and the antibiotic program is continued for another 30 days. If initial pyelograms demonstrate a moderate or advanced destructive process, then nephrectomy is performed after 10 days of antibiotic therapy and the regimen is continued through 90 days. All patients have check-up studies with x-rays at the completion of the antibiotic regimen and at 3 month intervals for the first year; every 6 months thereafter. Urine cultures and animal inoculation studies are carried out monthly for the first year.

RESULTS OF TREATMENT

Unilateral renal disease was treated in 42 patients (table 2). Sixty-seven per cent of this group had normal urine when last examined. Twenty-one of the unilateral cases were treated with nephrectomy as well as antibiotics and 86 per cent of these have remained well. An equal number of unilateral cases did not have surgery and lasting remission occurred in only 48 per cent. The results of medical treatment alone certainly do not compare favorably with the combined surgical and antibiotic regimen in this small group of cases; and the high failure

TABLE 2. *Unilateral renal disease*

	NUMBER OF PATIENTS	CONVERSION OF URINE TO NEGATIVE	% CONVERSION OF URINE TO NEGATIVE
No surgery			
Normal pyelograms	13	7	53 8
Minimal abnormality	4	2	50
Moderate abnormality	4	1	25
Total no surgery	21	10	47.6
Nephrectomy—all had abnormal pyelograms	21	18	85 7
Total all cases	42	28	66 7

rate in the cases showing normal pyelograms offer a strange paradox when compared to the high rate of remission that has been observed in the bilateral cases of the present series.

Table 3 summarizes the results of treatment in patients with bilateral renal tuberculosis. There were 30 patients in this group and 76 per cent have enjoyed remissions to date. The majority of these bilateral cases had one kidney removed either prior to the present program of antibiotic therapy or else in conjunction with the regimen. Table 4 enumerates the status of the kidneys in the bilateral cases in which surgery was not performed. It is of interest to note that 4 of 6 patients with significant bilateral pyelographic changes developed normal urine and have not relapsed. X-rays in 2 of these cases are of considerable interest so are included in this report (figs. 1 and 2).

Eighteen patients had negative kidneys but had tuberculous cystitis and/or genital involvement. Ten of these had a previous nephrectomy with the remain-

TABLE 3. *Bilateral renal disease*

	NUMBER OF PATIENTS	CONVERSION OF URINE TO NEGATIVE	% CONVERSION OF URINE TO NEGATIVE
Previous nephrectomy, normal x-ray	8	7	87.5
Previous nephrectomy, abnormal x-ray	5	4	80
Nephrectomy with treatment normal x-ray remaining kidney	4	3	75
Nephrectomy with treatment, abnormal x-ray remaining kidney	1	1	100
No surgery	12	8	66.7
Total	30	23	76 6

TABLE 4 *Bilateral renal disease without nephrectomy; results classified according to pyelographic findings*

PYELOGRAMS	NUMBER OF PATIENTS	CONVERSION OF URINE TO NEGATIVE	% CONVERSION OF URINE TO NEGATIVE
Normal to minimal abnormality on both sides	2	1	50
Normal to minimal abnormality on one side Moderate to advanced abnormality opposite side	4	3	75
Moderate to advanced abnormality on both sides	6	4	66.7
Total	12	8	66.7

TABLE 5. *Residual cystitis and/or genital tuberculosis*

	NUMBER OF PATIENTS	CONVERSION OF URINE TO NEGATIVE	% CONVERSION OF URINE TO NEGATIVE
Previous nephrectomy, normal x-ray	10	8	80
Normal x-rays, kidney urines negative	8	6	75
Total	18	14	77.7

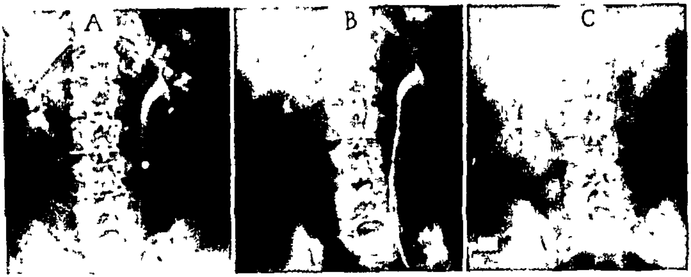

FIG. 1. V. T., a woman aged 29 with bilateral renal tuberculosis. History of pulmonary tuberculosis 1941; Potts's disease 1945. *A*, pyelogram, June 1948, prior to treatment. Patient was given streptomycin 2 gm. daily for 113 days (June-October 1948). Urine became negative after treatment and has remained negative until present time. *B*, 13 months after treatment. *C*, 4½ years after treatment. Note evidence of function on left side revealed by filling of micropelvis with excreted contrast medium. Patient has remained clinically well, and urine has been free from tuberculosis 4½ years.

ing kidney clinically free of disease. The remaining 8 patients had normal pyelograms as well as negative culture and guinea pig studies from both kidneys, yet had tubercle bacilli in the voided urine. Fourteen of these patients had a favorable response to therapy (78 per cent). The results are summarized in table 5.

SUMMARY OF RESULTS

Sixty-five of the 90 patients have had a conversion of urine to negative and have remained clinically free from urogenital tuberculosis 6 months to 6 years after treatment (table 6). Fifty-five had favorable response after one course of therapy, while thirty-five were initial failures or else relapsed after a temporary remission. Twenty-four of these 35 failures were given a second course of treatment and 9 became free from tubercle bacilli after treatment. Two patients received a third course of treatment and one of these exhibited negative urine after treatment (20 months at the present time), while the other relapsed 10 months after the third course of the antibiotic.

Streptomycin was used in 46 of the 116 courses of treatment and yielded a remission rate of 52.2 per cent, while 58.8 per cent of 70 dihydrostreptomycin courses resulted favorably. There is no significant difference in the 2 groups (table 7).

TOXICITY

Toxic manifestations in the 116 courses of therapy are summarized in table 8. In this series the incidence of reactions was materially greater with streptomycin although this antibiotic had the advantage of producing no apparent damage to the auditory branch of the VIII cranial nerve.

ANALYSIS OF FAILURES

In 25 cases the patients failed to respond favorably to therapy. This group represented 51 failures when measured in terms of total courses of treatment with or without nephrectomy. Table 9 shows the distribution of relapses by the month

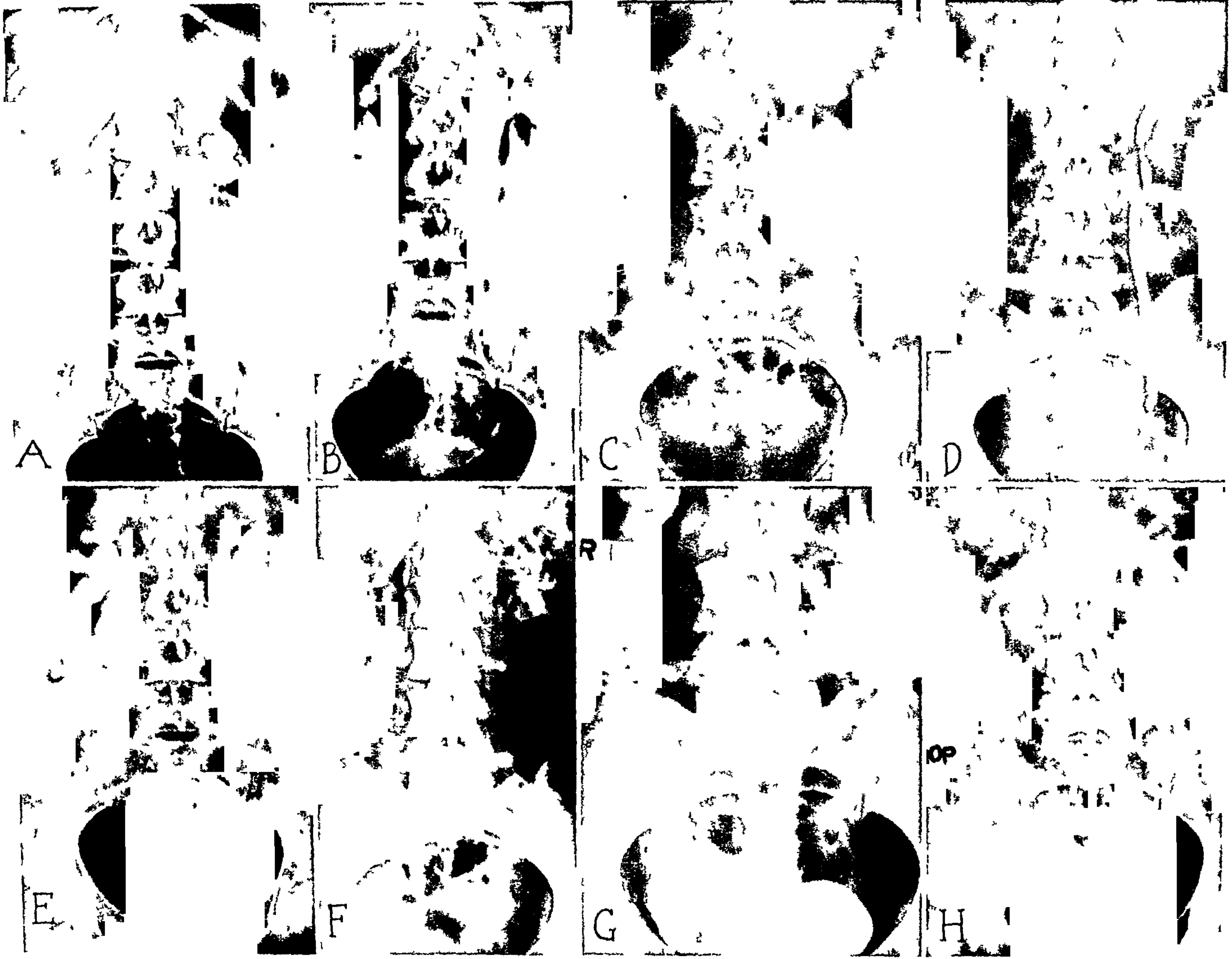
A
B
C
D
E
F
R
G
OP
H

Fig 2 L D, a woman aged 22 with bilateral renal tuberculosis proven by culture and guinea pig inoculation of urine from each kidney History of pulmonary tuberculosis *1943*, *tuberculous peritonitis* 1946 *A*, excretory urogram prior to admission to University Hospital *B*, retrograde pyelogram (University Hospital) June 1946 Bilateral disease Note constriction of left renal pelvis Patient received streptomycin *1 5 gm* daily for 70 days beginning June 1947 Urine normal at end of treatment *C*, excretory urogram, September 1947, at end of treatment Note bilateral hydronephrosis *D* retrograde pyelogram, September 1947 *showing nearly complete stenosis of* left pelvis Right cutaneous ureterostomy, September 1947, because of impassable stricture of right ureteral orifice *E*, retrograde pyelogram showing improvement of right hydronephrosis 1 month *following cutaneous ureterostomy* Note also marked improvement on left that has occurred in 1 month After 18 months on cutaneous ureterostomy, patient demanded that something be done to rid her of that unhandy device In April 1949 *right ureter* was reimplanted into bladder by attaching short upper ureter to tube fashioned from dome of bladder *F*, excretory urogram made 1 month following re implantation of ureter *G*, cystogram made 1 month *following re implantation of* ureter Note reflux *H*, excretory urogram, October 1952, shows no hydronephrosis in either kidney On left, upper calyx does not visualize but constrictive process that was present in pelvis in 1946 and 1947 *has cleared completely* Patient now clinically well, and urine has remained free from tuberculosis 6 years Patient married 2 years ago

TABLE 6. *Response of urinary tuberculosis to streptomycin and/or dihydrostreptomycin with or without nephrectomy (90 cases)*

	TOTAL	CONVERSION OF URINE TO NEGATIVE
First course	90	55
Second course	24	9
Third course	2	1
Total		65 = 72%

TABLE 7. *Results obtained in 116 courses of streptomycin or dihydrostreptomycin therapy*

	COURSES OF THERAPY	CONVERSION URINE TO NEGATIVE	FAILURE OR RELAPSE	% CONVERSION URINE TO NEGATIVE
Streptomycin	46	24	22	52.2
Dihydrostreptomycin	70	41	29	58.5
Total of all courses	116	65	51	56

TABLE 8. *Reactions to streptomycin and dihydrostreptomycin in 116 courses of therapy*

	COURSES OF THERAPY	VESTIBULAR	AUDITORY	ALLERGIC	% REACTION
Streptomycin					
Less 100 gm.	9	0	0	2*	22.2
100–200 gm.	27	13	0	1*	51.8
220–300 gm.	10	3	0	0	30
Total	46	16	0	3	41.3
Dihydrostreptomycin					
Less 100 gm.	14	4	1	1*	37.5
100–200 gm.	53	8	5	1*	26.4
200–300 gm.	3	0	0	0	0.00
Total	70	12	6	2	28.6
Total all courses	116	28	6	5	34.5

* Drug discontinued.

following completion of therapy. It would appear to be significant that the great majority of relapses occurred within the first 6 months, and that no relapses have occurred thus far after 10 months. In this connection it is of interest to note that in the group that Nesbit and Thirlby reported before this society 2 years ago, all of the patients who were then reported to be clinically free from urogenital tuberculosis have remained negative.

For purposes of analysis the 25 patients that failed to respond to treatment or relapsed can be divided into 3 groups:

1) Eleven patients had unilateral renal tuberculosis with normal or abnormal pyelograms on the affected side and were not operated upon. (Three since have had nephrectomy—within the past 6 months).

TABLE 9 *Time distribution of 51 relapses or failures*

• — First course
\ — Second course
* — Third course

Number of relapses	0	1	2	3	4	5	6	7	8	9	10	11	12
10													
9	\												
8	\		\		\								
7	•		\		•								
6	•	\	\	\	•		*						
5	•	\	•	\	•		\						
4	•	•	•	•	•		\						
3	•	•	•	•	•		•	\	•				
2	•	•	•	•	•		•	\	•				
1	•	•	•	•	•		•	•	•		•		

Months following therapy

2) Seven with normal kidneys or who had nephrectomy and antibiotics for treatment of unilateral disease remained positive due to persisting cystitis and/or genital tuberculosis

3) Seven patients with bilateral disease

SUMMARY

In a series of 90 patients with urogenital tuberculosis, 72 per cent (65 cases) have exhibited negative urine for 6 months to 6 years following the completion of therapy

A therapeutic program of 2 0 gm a day of streptomycin or dihydrostreptomycin for 90 days with sanatorium care 6 to 12 months has been used and still is advocated, along with the uses of PAS and isoniazid It is our purpose to continue with this plan of therapy in the hope that a comparison with reports of other series of patients who are treated with other programs may eventually reveal just what plan of treatment is the best in yielding long term results

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A TECHNIQUE FOR INTERMITTENT OR CONTINUOUS IRRIGATION OF THE RENAL PELVIS

JAMES H. SEMANS* AND HENRY F. LaGUETTE

Certain factors are desirable in any technique for intermittent or continuous irrigation of the renal pelvis, especially when solutions of low pH are used. The fever produced should be minimal. The procedure should not affect permanently the caliber of the ureter or the function of the kidney. The pain should not be sufficient to require deep narcosis. The unanesthetized, hospitalized patient should be able to perform the irrigation with safety, and without constant supervision, over a period of several days.

Since 1945, one of us (J. H. S.) has been using a method which is reported here because it has met these requirements. Six patients performed the irrigation on 11 occasions. The febrile reaction was mild. There was no evidence of late or permanent renal damage demonstrable by microscopic examination of a kidney removed 2 years after irrigation (case 6). The excretion of phenolsulfonphthalein increased; and the nonprotein nitrogen in the blood was not elevated. After the patient learned the amount of irrigating fluid tolerated the pain was usually controlled by codeine in dosage of ½ or 1 grain. Demerol and morphine were used as indicated. There was no constant supervision necessary. As much as 500 cc of solution M[1] passed through the renal pelvis in 24 hours. Pyelograms made after irrigation demonstrated no ureteral stricture, with the exception of one case in which hydro-ureter was present before irrigation.

The indications for irrigation were small residual calculi impacted in a calyx (cases 1, 2, 3, 4 and 5), incrusted pyelitis diagnosed at the time of removal of large phosphatic calculi (cases 3, 4 and 5) and chronic symptomatic pyelonephritis, refractive to prolonged and repeated antibiotic therapy (case 6). Irrigation was always used as an adjunct to the usual therapeutic measures. Citric acid adjusted to pH 4.5 was alternated with normal saline. The gross character of the urine changed from cloudy to clear approximately a week following completion of the procedure. This improvement was always temporary and could have been attributed to the antibiotics.

PREPARATION OF THE PATIENT

One week before irrigation, the patient is studied by means of urine culture, tube sensitivity test, determination of the nonprotein nitrogen of the blood and by excretion of phenolsulphonphthalein for a period of 2 hours, at half-hour intervals.

The tube sensitivity test is used to select the antibiotic always given to prevent fever and bacterial contamination of the blood stream during irrigation. If this test is not available, a combination of penicillin and streptomycin is injected before pyelography and continued once or twice each day, until the patient can

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Read at annual meeting, Southeastern Section of American Urological Association, Havana, Cuba, March 26-29, 1953.

* Present address: Duke Hospital, Durham, N. C.

take medication orally Chloromycetin can then be given by mouth in dosage of 500 mg every 8 hours These drugs prevent the blood culture from becoming positive and minimize the mucus and pyelonephritis associated with the procedure Their administration is begun one day before the irrigation and is continued afterward until the patient remains afebrile without them for at least 48 hours

Determination of the nonprotein nitrogen and excretion of phenolsulphonphthalein before the irrigation is useful for comparison with values obtained afterward

TECHNIQUE

A No 5 graduated opaque catheter with whistle tip is passed to the renal pelvis A stylet of wire remains in place, with the tip withdrawn 10 cm from the end lying in the kidney The wire is forcibly bent at a sharp angle over the end of the catheter and cut off a few millimeters beyond the angled end See figures 1 and 2 After x-ray films have shown the tip of the catheter in the center of the renal pelvis, or any other desired area, the bladder is emptied and the cystoscope removed Care is taken to avoid moving the catheter during this maneuver

A No 20 Foley-Alcock catheter with 5 cc bag is next placed in the bladder and the balloon inflated Another x-ray film is exposed, since it is essential that the catheter in the ureter be left in the exact position required

The two catheters are then fastened together A silk ligature is tied tightly around the Foley-Alcock catheter and then around a narrow strip of adhesive,

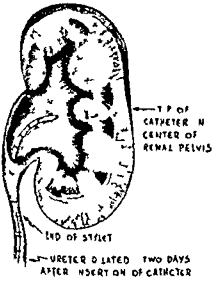
TIP OF CATHETER IN CENTER OF RENAL PELVIS
END OF STYLET
URETER DILATED TWO DAYS AFTER INSERTION OF CATHETER

FIG 1

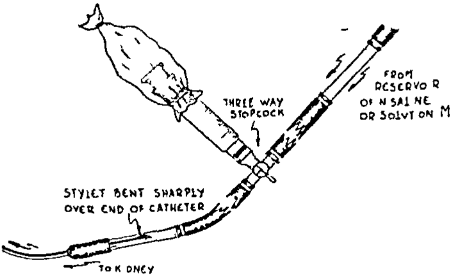
FROM RESERVOIR OF N SALINE OR SOLVENT M
THREE WAY STOPCOCK
STYLET BENT SHARPLY OVER END OF CATHETER
TO KIDNEY

FIG 2

FIG 1 Schematic drawing of renal pelvis containing No 5 graduated opaque catheter with whistle tip Stylet of wire is 10 cm from end of catheter, which lies in center of renal pelvis

FIG 2 Detailed drawing of inset marked in figure 3 by heavy black circle Small surgical drain of Latex is ligated on one end, stretched and ligated around 2 cc syringe having Luer lok After sterilization syringe is attached to 3 way stopcock, which is interposed by Latex and glass adapters into irrigation system, next to ureteral catheter leading to kidney Perforated small rubber tip, standard accessory of cystoscope, is used on ureteral catheter This apparatus enables patient to introduce either sterile saline, or solution on clinical trial as solvent through ureteral catheter into renal pelvis intermittently, as tolerated Later stopcock is set for continuous flow (see text under technique of irrigation)

3 mm. in width, which, in turn, is wrapped around the catheter coming from the ureter. Next, the long ends of the same silk ligature are tied over the adhesive now covering both catheters. The same procedure is repeated on both catheters a few centimeters distally. It is our experience that this method prevents any but the slightest change in the catheter's position in the kidney during the entire period of irrigation. The catheter in the urethra is then fixed to the penis with adhesive tape.

For the first 2 days, the patient is instructed to distend the pelvis with 2 cc of sterile normal saline solution intermittently (fig. 3). He soon learns to increase the amount, without producing renal pain. The fluid is injected by means of the aseptic closed apparatus illustrated in the drawing (fig. 2).

Five cubic centimeters of sterile indigo carmine solution is added to the reservoir of normal saline. After 2 or 3 days, the fluid coming from the catheter in the bladder becomes blue. This is an indication that the ureter has dilated sufficiently around the inlying catheter to accommodate a continuous flow. A rate of 60 drops per minute is tolerated.

Once this has occurred, the more irritating solution M is introduced. It is used alternately with the saline solution, frequently enough to prevent renal pain. A total of 500 cc of solution M can be tolerated in the pelvis during 24 hours. As soon as pain begins, solution M is stopped, and saline solution substituted. The discomfort should not exceed the therapeutic effect of 1 grain of codeine. Mucoid detritus may occlude the catheter in the urethra and necessitate removal by the usual technique of irrigation.

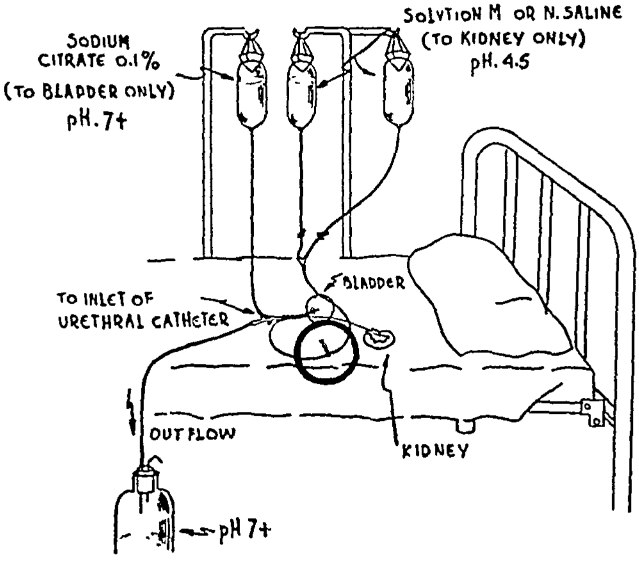

FIG. 3. On far right is reservoir for normal saline solution. Patient can regulate flow by screw clamp. A y-tube separates this solution from solution M or other solvent in next reservoir to left, so that patient can substitute either solution for the other, in case renal pain occurs with continued introduction of solvent. Reservoir on far left supplies alkaline solution (sodium citrate) to raise pH of vesical contents. Solution flows continuously through inlet tube into bladder at a rate controlled by patient with screw clamp. Patient introduces fluid into kidney intermittently, at first, by syringe illustrated in detail in figure 2.

Sodium citrate, 0.1 per cent, runs continuously into the inlet tube of the Foley Alcock catheter (fig. 3) at a rate of flow sufficient to raise the pH of the vesical urine to 7 (checked with nitrazine paper by the patient). This minimizes pain in the bladder.

CASE ABSTRACTS

Case 1. J. J. A., McGuire General Hospital, Richmond, Va., registration No. 1900, admitted February 28, aged 48 years. Diagnosis: Calculus, calyceal, left kidney, following pyelolithotomy. Duration of irrigation: 7 days. Comment: Pyelogram made 1 week and 3 months after irrigation showed no evidence of calculus.

Case 2. R. C. S., McGuire General Hospital, Richmond, Va., registration No. 5005, admitted 1945, aged 19. Diagnosis: Calculi, miliary, multiple (prolonged recumbency). Duration of irrigation: 5 days. Comment: No improvement. After ambulation, patient passed many calculi. Only one opaque shadow remained.

Case 3. H. A. F., Piedmont Hospital, Atlanta, Ga., registration No. 114818, admitted January 8 through January 18, 1950, aged 47 years. Diagnosis: 1) Solitary kidney; 2) incrusted pyelitis (observed at time of removal of large staghorn calculus). Duration of irrigation: 6 days. Amount used: 3000 cc solution M. Highest temperature recorded: 99F. Antibiotic given: Chloromycetin. Laboratory data: Nonprotein nitrogen, 34.1 mg. per cent, before irrigation, 30.0 mg. per cent, after irrigation; phenosulfonphthalein output, 64 per cent in 2 hours, 11 months after irrigation.

Second irrigation: Admitted August 9 through August 19, 1950. Diagnosis: Small recurrent calculi (two) in solitary kidney. Duration of irrigation: 5 days. Amount used: 3000 cc solution G. Highest temperature recorded: 99F. Antibiotic given: Penicillin, streptomycin and chloromycetin. Laboratory data: Nonprotein nitrogen, 23 mg. per cent, before irrigation; phenolsulfonphthalein output, 52 per cent in 2 hours, 8 months after irrigation.

Third irrigation: Admitted: March 11 through March 24, 1951. Duration of irrigation: 6 days. Amount used: 3000 cc solution G. Highest temperature recorded: 99F. Antibiotic given: Chloromycetin. Laboratory data: Nonprotein nitrogen; 34.8 mg. per cent, before irrigation, phenolsulfonphthalein, 56 per cent in 2 hours, before irrigation, 52 per cent after irrigation.

Fourth irrigation: Admitted: August 30 through September 11, 1952. Duration of irrigation: 5 days. Amount used: 3000 cc of solution G. Highest temperature recorded: 99F. Antibiotic given: Chloromycetin. Laboratory data: Nonprotein nitrogen, 25 mg. per cent; phenolsulfonphthalein, 66 per cent in 2 hours, before irrigation.

Case 4. J. M. M., St. Joseph's Infirmary, Atlanta, Ga., registration No. 5246, admitted November 30 through December 13, 1949, aged 27 years. Diagnosis: 1) Calculus, left kidney; 2) pyelonephritis, chronic. First irrigation: Duration, 6 days. Amount used: 3000 cc solution G. Highest temperature recorded: 100.2F. Antibiotic given: Chloromycetin. Laboratory data: Phenolsulfonphthalein output, 45 per cent in 2 hours, 6 months before irrigation; 59 per cent in 2 hours, 2 years after irrigation; 68 per cent in 2 hours, 3 years after irrigation.

Second irrigation: Admitted: August 14 through August 27, 1952. Duration of irrigation: 6 days. Amount used: 3000 cc solution G. Highest temperature recorded: 100F. Antibiotic given: Chloromycetin.

Case 5. M. L., Piedmont Hospital, Atlanta, Ga., registration No. 119788, admitted September 10 through September 22, 1950, aged 43 years. Diagnosis: Calculi, left kidney. Duration of irrigation: 5 days. Amount used: 1000 cc in 48 hours (solution G). Highest temperature recorded: 101F. Antibiotic given: Chloromycetin. Narcotics used: Codeine, ½ grain; Demerol, 100 mg.; morphine, ⅙ grain. Laboratory data: Nonprotein nitrogen, 23 mg. per cent, 1 month before irrigation, 34 mg. per cent, 2 years after irrigation; phenolsulfonphthalein, 47 per cent in 2 hours, before irrigation; 64 per cent in 2 hours, 2 years after irrigation.

Case 6. J. L. H., St. Joseph's Infirmary, Atlanta, Ga., registration No. 4918, admitted September 11, 1950, aged 46 years. First irrigation: Diagnosis: chronic pyelonephritis, symptomatic. Duration of irrigation: 10 days. Amount used: 3000 cc solution G. Highest temperature recorded: 100.4F. Antibiotic given: Chloromycetin. Narcotics given: Demerol, 100 mg. Laboratory data: Nonprotein nitrogen, 24.5 mg. per cent, last day of irrigation; phenolsulfonphthalein output, 29 per cent in 2 hours, 2 years after irrigation.

Second irrigation: Admitted: July 8 through August 2, 1952. Amount used: 1000 cc solution G. Duration of irrigation: 5 days. Highest temperature recorded: 101.2F and 102.8F. Antibiotic given: Penicillin, streptomycin and terramycin. Laboratory data: Nonprotein nitrogen, 30 mg. per cent, before irrigation; phenolsulfonphthalein output, 29 per cent in 2 hours, before irrigation, 47 per cent in 2 hours, 12 days after irrigation. Nephrectomy: 2 weeks after irrigation. Microscopic diagnosis: Low grade pyelonephritis (St. Joseph's Infirmary, Path. No. 12317). Comment: Indication for nephrectomy: Persistent nephritis, febrile, symptomatic, refractive to antibiotics for 2 years.

DISCUSSION

This technique for irrigation of the renal pelvis has proved valuable in the clinical trial of solvents for certain types of urinary calculi. Except for the disappearance of small calcified shadows in 2 cases, no dissolution was evident in the other patients.

In one of these, a calculus was passed soon after completion of irrigation. Approximately 1 week after irrigation, urine, which had been grossly cloudy and mucoid previously, became temporarily clear. Since antibiotics were used in all patients, this improvement could not be attributed to the procedure of irrigation.

Suby[1] has stated that a solvent is relatively impractical unless a calculus can be completely dissolved in 50 to 75 hours. This technique would comply with this requirement, since the irrigation continued over a period of 48 hours to 10 days. Clinical reports of the use of solutions now available, such as G, M and Versene, do not indicate that these agents can be successful in any significant number of cases. However, the value of solution G in the dissolution of vesical incrustation,

[1] Suby, H. I.: Dissolution of urinary calculi. J. Urol., **68:** 96, 1952.

can often be confirmed by cystoscopy For this reason, it was used when incrusted pyelitis was observed at the time of operation for removal of the calculus

The principle of using a dilated ureter to drain irrigating fluid from the renal pelvis, was illustrated by Kelly and Burnam (drawing by Max Brodel) in 1922 [2]

SUMMARY

A technique for irrigating the renal pelvis by intermittent or continuous flow, is described for clinical trial of solvents of urinary calculi

It is recommended for cases of minimal fever when antibiotics preceded and followed irrigation The renal function and caliber of the ureter were not damaged by the procedure The pain was usually controlled by codeine The hospitalized patient was able to perform the irrigation with safety and without constant supervision, over a period of several days

[2] Kelly and Burnam Diseases of the Kidney, Ureter and Bladder Philadelphia D Appleton & Co 1922, vol II, p 208

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LEUKOPLAKIA OF RENAL PELVIS AND URETER

CHARLES C. FALK

Leukoplakia of the urinary tract has long been recognized, but its occurrence in the renal pelvis or ureter has been so infrequent that we should accept every opportunity to obtain a better understanding of this curious tissue response. Since 1882, when Epstein apparently described it for the first time, less than 100 cases involving the renal pelvis and ureter have been presented (McCrea; Keesal and Rosner). It seems worth while to add another case and to review briefly the present concepts of the disease.

Leukoplakia is a metaplastic change in the urinary tract in which the normal transitional epithelium is changed into the squamous or skin-like type, characterized by keratinization and almost always by desquamation. Writers generally agree that the lesion is precancerous.

CASE REPORT

A well developed man of 35, married, and the father of four, employed as a stationary engineer on a logging operation, for the past 15 years had suffered intermittent attacks of colicky pain in the left flank, radiating downward along the course of the ureter. Several urological studies during the past 10 years had failed to reveal the cause of this pain. Meanwhile the attacks were occurring more frequently, and were becoming increasingly severe and incapacitating. He had just had an episode of this pain for about a week. There was no dysuria, frequency, nor hematuria, but he stated that the urine was always cloudy, even in teh interval between the attacks of colic.

The physical examination revealed nothing outside the urinary tract. The urine was grossly hazy, had a pH of 6, a specific gravity of 1.020, and contained neither albumin nor sugar. The sediment showed 15 pus cells per high dry field and many strips and flakes of squamous epithelium. The Wassermann was negative and the blood count entirely normal. Nonprotein nitrogen was 32, and the bleeding and clotting times normal.

The 24F cystoscope was introduced easily and immediately a pearl gray membrane was seen covering almost the entire trigone. The ureteral orifices were not involved, but were somewhat reddened and edematous. On attempting to catheterize the left ureter, an impermeable obstruction was met at 10 cm. above the orifice (figs. 1 and 2). Indigo carmine injected appeared in four minutes, but with poor concentration.

Pyelo-ureterograms revealed several filling defects in the left ureter and an irregular and motheaten appearance. The capacity of the renal pelvis was increased and the terminal calyces were somewhat blunt. The urine from the left kidney showed no acid fast bacilli and the guinea pig inoculation was negative for tuberculosis. Culture of this urine revealed a mixed growth of Escherichia

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Read at annual meeting, Western Section of American Urological Association, San Francisco, April 27–30, 1953.

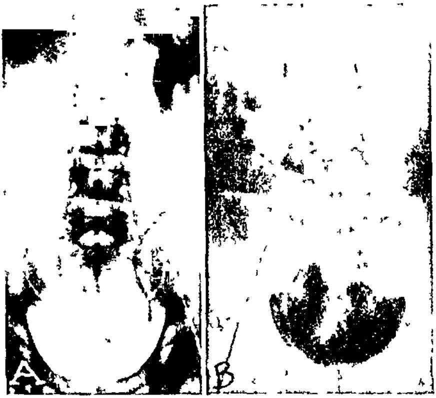

FIG. 1 *A*, pyelo-ureterogram printed in positive showing moderate calyceectasis and pyelectasis; tortuosity of ureter with filling defects *B*, same as *A*, but printed in negative

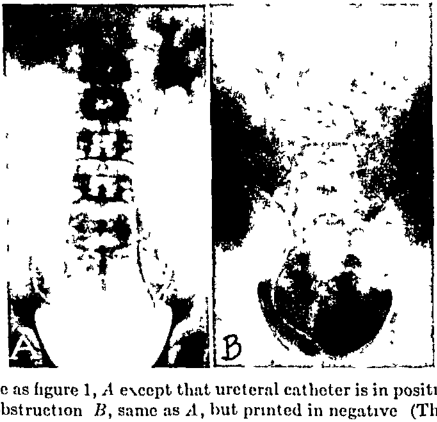

FIG 2 *A*, same as figure 1, *A* except that ureteral catheter is in position to indicate level of impermeable obstruction *B*, same as *A*, but printed in negative (These x-rays are used mainly to point out that urographic findings by means of technique used are not characteristic in leukoplakia)

coli and Staphylococcus aureus. The presumptive diagnosis was made of leukoplakia of the urinary bladder and neoplastic involvement of the left ureter with obstruction to the left kidney.

A ureteronephrectomy was performed The lower ureter, together with a cuff of the bladder, was first excised. The kidney was then removed through the usual lumbar incision. The gross specimens are shown in fig 3. The pathologist, made the following diagnoses: 1) leukoplakia of the renal pelvis and ureter; 2) acute pyelonephritis; 3) cortical cysts of the kidney (fig. 4).

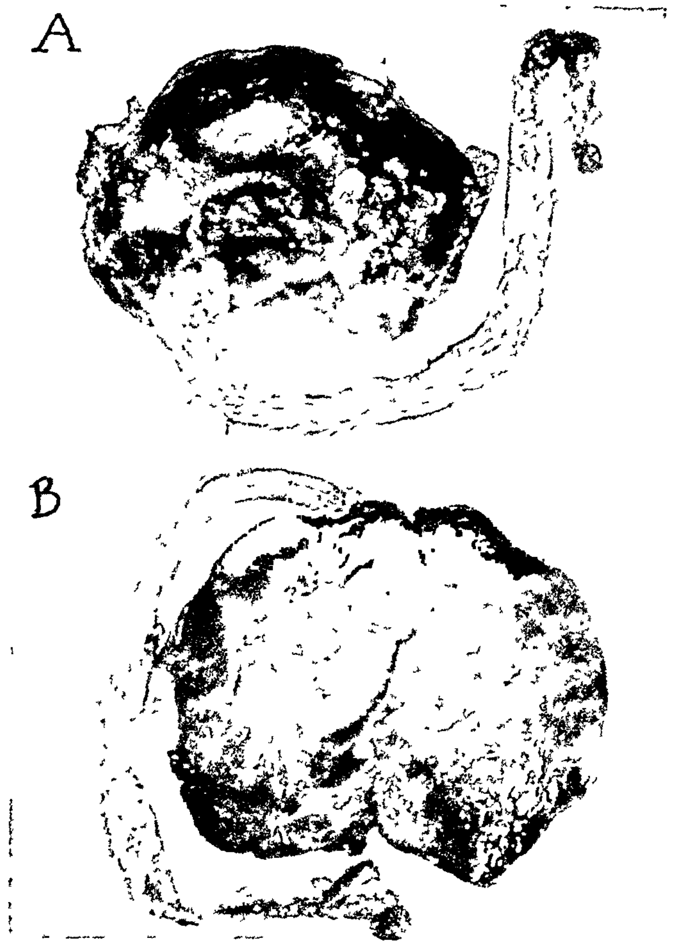

Fig 3. *A*, gross surgical specimen consisting of kidney, ureter and portion of bladder. Ureter has been sectioned longitudinally showing pathologic skin-like structure of upper two thirds of ureter and pelvis. *B*, same as *A* except that kidney and pelvis have been sectioned as well showing extensive involvement which affects entire pelvis.

Recovery was without incident and the patient left the hospital on the twelfth postoperative day. He was examined every 2 weeks for the succeeding 4 months. The pyuria was greatly improved, though the urine continued to be grossly hazy and flakes of epithelium were still present. He regained his original weight in 2 months and had resumed his occupation.

DISCUSSION

The cause of leukoplakia is unknown. Undoubtedly the most widely accepted explanation is that leukoplakia of the urinary tract is a true metaplasia arising as the result of chronic inflammation and irritation, and is the biological process of adaptation to environment in the form of protective cornification (Hinman, Kutzmann and Gibson). In the study of a larger series of cases two uniform observations have been made: 1) pyuria is present in all cases, and 2) leukoplakia usually occurs concomitantly with other diseases. It is suggested, there-

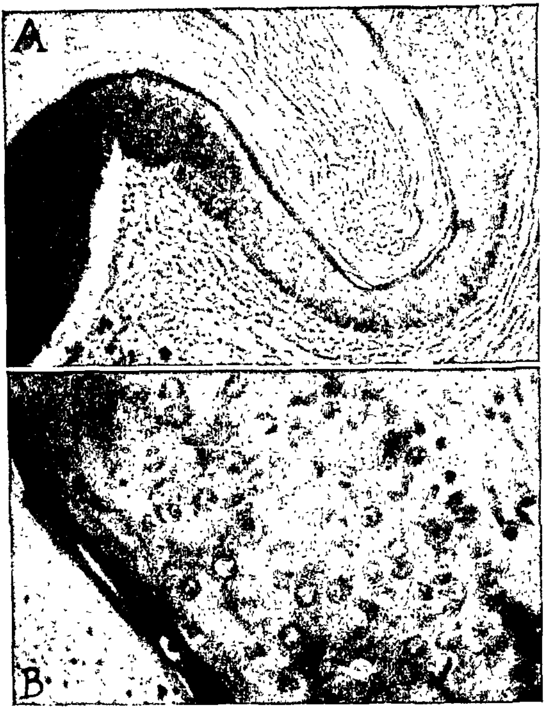

FIG. 4. *A*, cornified stratified squamous epithelium has completely replaced transitional epithelium which normally lines ureter. Note thick layer of desquamated epithelial cells on epithelial surface. H and E stain. *B*, same as *A*, but higher magnification to show cellular details.

fore, that the leukoplakia may be secondary to severe chronic infection, calculous or neoplastic disease, or urinary tract obstruction. It is no longer believed that it is a manifestation of syphilis. While there once appeared to be laboratory evidence that a lack of vitamin A was causative, this view seems to have been abandoned (Senger, Bottone, and Kelleher).

The disease occurs most commonly in the age group between 30 and 50. There are few patients under 20, although occasional cases have been reported in childhood and also in extreme old age. This would lead to the conclusion that any hypothesis that the etiology of the disease is based on embryonal cell rests is untenable. The condition is found about twice as often in the male as in the female (Laughlin and Bilotta).

There are no symptoms typical or characteristic of this condition except as a rule those of the coexisting disease. Frequency, urgency, dysuria, hematuria, any or all may be present. In my patient ureteral colic was the predominant complaint. The outstanding finding noted by several authors is the discovery of cornified epithelium in the urinary sediment. It is described by Senger, Bottone, and Kelleher as the passage of "gritty flakes in the urine." It is also mentioned by Laughlin and Bilotta, and Arnholdt considers it pathognomonic, though he points out that the disease may exist without this finding. It was certainly prominent in the present case.

The difficulty in preoperative diagnosis is evidenced in the cases reported. Subjective symptoms are of little value, and one must re-emphasize the one important objective clue, the finding of large amounts of squamous epithelium in the urinary sediment. This observation should suggest leukoplakia at once. I certainly believe also that if leukoplakia is seen cystoscopically in the bladder, it should be considered possible, or even likely, that the disease may also affect the upper urinary tract. Kretschmer suggested this fact some years ago.

Pyelo-ureterographic findings are certainly not diagnostic in this disease and are only of general value. All writers agree on this point except Arnholdt, who was able to demonstrate, by the use of a dilute medium for pyelography, an x-ray silhouette which he considered consistent with the leukoplakic folds and wrinkles in the mucosa of the kidney pelvis. His description did not apparently impress the later writers.

One author described passing a cystoscopic rongeur into the lower ureter and obtaining a biopsy specimen from which a positive diagnosis was made. While the use of the technique must certainly be limited, its possibility might well be remembered.

Leukoplakia in the upper urinary tract must be differentiated from tuberculosis, neoplastic disease, either squamous or transitional in type, calculosis, severe pyogenic pyelonephritis, and pyelitis and ureteritis cystica and glandularis (Stirling and Ash).

The treatment of leukoplakia involving the kidney and ureter is preferably ureteronephrectomy, both to remove the potential malignancy and to relieve the symptoms. Fortunately in less than 5 per cent of the patients the condition has been bilateral and only conservative palliative measures could be instituted. In the light of our present knowledge such therapy must be directed toward control of infection and promotion of free drainage.

SUMMARY

Leukoplakia of the renal pelvis, ureter, or both, is rare, less than 100 cases having been reported in the last 80 years.

Leukoplakia in the urinary tract is a precancerous lesion.

The etiology is obscure, but the evidence strongly supports the concept that the causative factor is prolonged irritation in the form of chronic infection.

Leukoplakia is usually concomitant with other diseases.

Preoperative diagnosis of leukoplakia of the kidney or ureter is seldom made, but the disease should be suspected when the cystoscopic findings are inconclusive and there are masses of squamous epithelial cells in the urinary sediment.

When leukoplakia can be seen in the bladder through the cystoscope and there is any evidence of disease in the upper urinary tract, the same condition in the kidney and ureter should be considered a strong possibility

Treatment is ureteronephrectomy when leukoplakia involves the kidney and ureter and is unilateral, as it is in more than 90 per cent of the cases.

Eureka, Calif.

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SCHWANNOMAS

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Schwannomas, or, as they are often called, neurinomas or perineural fibroblastomas, arise from the sheath of Schwann, usually from a peripheral nerve. The commonest nerve to be involved is the acoustic nerve.

In reviewing the literature, such a tumor in the retroperitoneal space in close association with the kidney and ureter has not been recorded. The commonest retroperitoneal tumors arising in this region have been reported by Donnelly and Judd. Whether schwannomas in this region have not been recognized or whether they have been confused with the more common tumors such as sarcomas, fibrosarcomas, neuroblastomas, sympathicoblastomas, sarcomas and cystic tumors one cannot proffer an excuse. Frank described a cystic schwannoma containing five or six ounces of clear fluid which arose from low down in the pelvis and had to be differentiated from an ovarian cystic tumor. So far as the literature is concerned, urologists have not before encountered schwannomas which produced urinary tract changes. The authors wish to report two cases of schwannoma, both in female adults, one a solid, relatively benign tumor and the other cystic, with a relatively high degree of malignancy.

CASE REPORTS

Case 1. A white woman, aged 31 (Mrs. E. D., Unit No. C 55562), was admitted to the Urological Service of the New Haven Hospital on April 12, 1951, complaining of a feeling of fullness in the epigastric region for a period of 1 month. She was in the third month of her second pregnancy. She denied any nausea, vomiting or urinary symptoms. She had never had any hematuria. Her family history was irrelevant, and her past history showed good health respective to all systems and one pregnancy which had terminated normally 19 months previously. The family history disclosed that her father died at 66 years of leukemia and asthma and that her mother had been operated upon for a myoma of the uterus. Her general condition was good. Physical examination revealed that the left side of the abdomen was larger than the right. A mass was palpable in the left flank extending from under the costal cage down to the crest of the ilium, smooth in contour, soft in consistency and not particularly tender. The pelvic examination was compatible with the stated pregnancy. Cystoscopic examination showed a normal bladder. The bladder urine was clear in color; pH, 5.5; specific gravity, 1.010; albumin, 0; sugar, 0; microscopic examination showed no pus cells or red blood cells. The urines from the right and left kidneys were normal. Cultures of the urine from each kidney and the bladder were negative for bacterial growth. The renal function test with phenolsulfonphthalein disclosed 25 per cent from the right kidney and 20 per cent from the left kidney in 15 minutes. Bilateral retrograde

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Read at annual meeting, American Association of Genito-Urinary Surgeons, Hot Springs, Va. May 6–8, 1953.

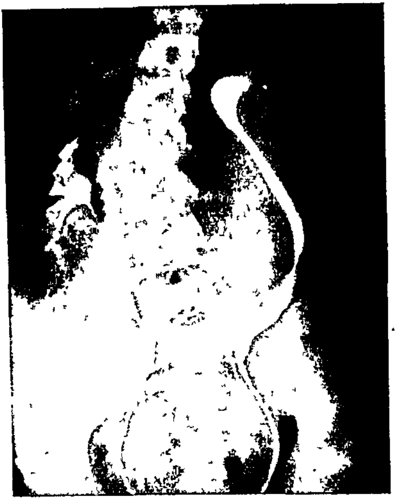

FIG. 1. Case 1. Retrograde pyelogram showing left ureter taking lateral, curved course with dilatation of upper two-thirds. Slight dilatation of pelvis with delicate calyces and high position of kidney.

pyelograms (fig. 1) revealed a normal right kidney, pelvis and ureter. On the left, the ureter took a normal course up to the pelvic brim, swept laterally and posteriorly and returned to the left paravertebral region at the level of the first lumbar vertebra, where the ureter was moderately dilated between the pelvic brim and the renal pelvis. The major and minor calyces of the left kidney were outlined, showed no evidence of dilatation and were less filled than the calyces on the right. The lower and middle calyces were displaced upward and were crowded together as the result of displacement by a large, space-occupying lesion of the lower pole of the left kidney which also displaced the ureter posteriorly and laterally. This large, soft-tissue density showed smooth edges with regular outline and no evidence of calcification and was thought probably to represent an enlarged cyst of the lower pole of the left kidney. The chest x-ray revealed normal bony thorax, diaphragm, heart and mediastinal contents with clear lung fields. The differential diagnosis preoperatively was between 1) retroperitoneal tumor, 2) hydronephrosis of the lower half of the kidney and 3) solitary cyst of the kidney.

Treatment:—On April 17, 1951, the left flank was explored through a lumbar incision. A large tumor shaped like a football was located below the left kidney but not attached to the kidney. Its surface was smooth, solid in consistency and adherent to the posterior abdominal wall and to the descending aorta. The tumor was carefully dissected free and removed. There were not any lymph node involvements. The retroperitoneal space was drained with a cigarette Penrose drain The patient was discharged from the hospital on the eleventh day after operation in excellent condition and with the wound completely healed.

The pathological report of the tumor (fig. 2) removed is as follows:

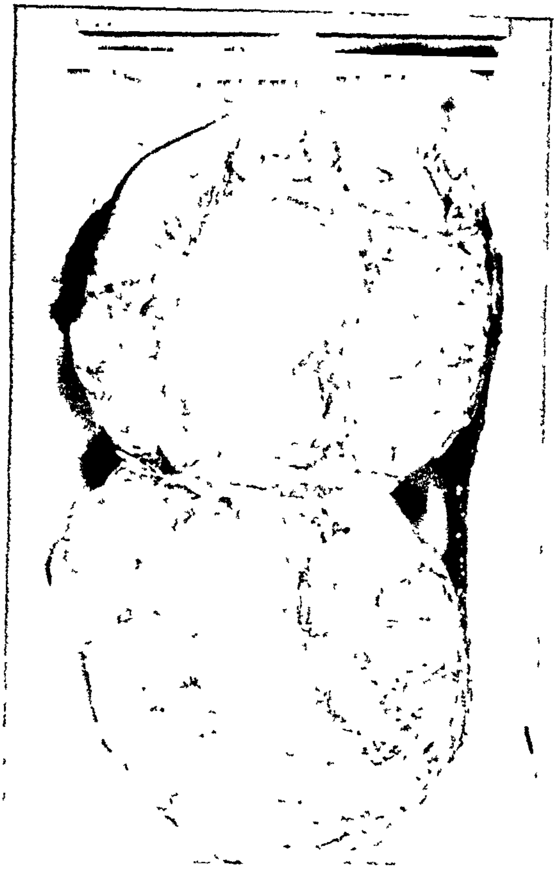

FIG. 2. Case 1. Cross section of solid schwannoma which is well encapsulated

"The tumor is lemon shaped, measuring 17 cm. by 13 cm.; total weight is 1680 gm. Its surface is covered by fascia which can be stripped from the tumor with only slight difficulty, leaving a shiny, yellow and gray glistening surface. The cut surface of the tumor is yellowish-gray in color, soft in consistency and cystic. The microscopic sections show connective tissue containing areas of dense bundles of fibrous-like cells with long, narrow, elongated blue nuclei (fig. 5, *A*). These bundles of tissue seem to interweave, and in some areas the nuclei give the impression of palisading. In other areas loose connective tissue is present. The connective tissue gives the general appearance of having been fatty tissue. In other areas of this connective tissue many round, blue-staining cells are seen which may be chronic inflammatory cells. A large number of small-sized blood vessels are also seen in the tissue. Pathological diagnosis: Schwannoma."

This patient made an uneventful recovery from the operation and 7 months later delivered a normal boy. Six weeks after the operation an excretory urogram revealed slight dilatation of both ureters and pelves, but otherwise the urinary tract was normal.

Case 2. A white woman, aged 33, was admitted to the Urological Service of the Grace-New Haven Community Hospital on November 7, 1948. Her complaints were numerous and varied. She complained of vague abdominal discomfort which was not associated with meals. She had bouts of bronchial asthma. Her previous hospital admissions were numerous, and her symptoms were explained on the basis of allergy. Physical examination revealed this patient to have marked scoliosis and lordosis of the thoracic and lumbar vertebrae, a deformity which had been present since birth. Abdominal examination revealed a palpable mass in the left flank, smooth in contour and solid in consistency, which was thought to be a palpable left kidney as a result of displacement caused by the associated scoliosis. The bladder urine was normal, and microscopic examination showed no evidence of pus cells or red blood cells. The urine from each kidney was normal, and the culture from each kidney was negative for bacterial growth. The function of each kidney as measured by the phenolsulfonphthalein test was within normal limits. Bilateral pyelo-ureterograms showed a marked axial torsion of the lower pole of the left kidney caused by a large, well-defined mass below the lower pole of the left kidney (fig. 3). The differential diagnosis was between a tumor of the lower pole of the kidney and a primary retroperitoneal tumor, extrarenal in origin.

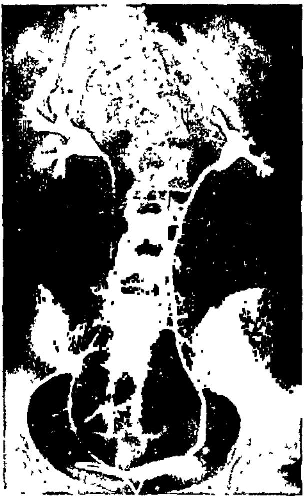

FIG. 3. Case 2. Retrograde pyelogram showing axial torsion of left kidney caused by mass located below kidney and medial deviation of course of ureter.

Treatment:—At operation, a modified left kidney incision was made below and parallel to the twelfth rib and extending towards the umbilicus in a transverse direction. The retroperitoneal space was opened and a large tumor was located extending from the level of the lower pole of the kidney to the crest of the ilium. The tumor was the size of a grapefruit and seemed to be attached medially to the vertebral column. Anterior to it was found a large band of nerve tissue about half an inch in width. The tumor, which was solid in consistency and encapsulated, was excised conserving the kidney.

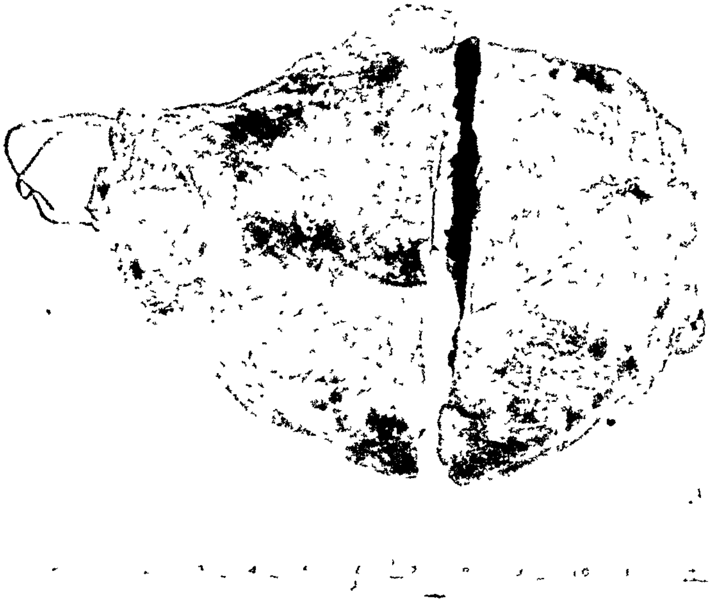

FIG. 4. Case 2. Thick-walled, cystic schwannoma

The pathological report is as follows:

"A thick-walled, cystic tumor (fig. 4), the size of a small grapefruit. The surface is roughly nodular. Cross section of the mass reveals it to be solid with a large area of degeneration and cyst formation. A large nerve trunk issues from *one pole of the tumor mass.* Microscopic pathological diagnosis: Cystic schwannoma of a retroperitoneal tumor." See figure 5, *B*.

The patient made an uneventful recovery from surgery and was discharged from the hospital 2 weeks later. Three months after the operation she had gained 13 pounds in weight. On July 5, 1949, eight months after surgery, she again began complaining of pain in the left flank accompanied by nausea. She was re-admitted to the hospital on August 18, 1949, complaining of more severe pain in the left upper quadrant of the abdomen accompanied by nausea and vomiting. She had also noted a localized swelling between the eighth and ninth ribs in the left anterior axillary line. Abdominal examination revealed in the left upper quadrant a firm mass measuring about 5 by 6 cm., which did not move with respiration. X-ray study of the chest revealed erosion of the anterior one-third of the left seventh rib at the anterior axillary line and extending from this ragged anterior margin of the seventh rib a large, soft-tissue mass measuring approximately 5 by 7 cm. in diameter. Excretory urograms revealed a normal right kidney, pelvis and ureter. There was no evidence of excretion of dye by the left kidney.

Cystoscopic examination was done, and both ureters were catheterized. Bilateral pyelograms showed failure of the left urinary tract to fill above the fifth lumbar vertebra where a soft-tissue mass could be seen to the left of the vertebral column at the level of the fourth and fifth lumbar vertebrae. The right kidney, pelvis and ureter were normal.

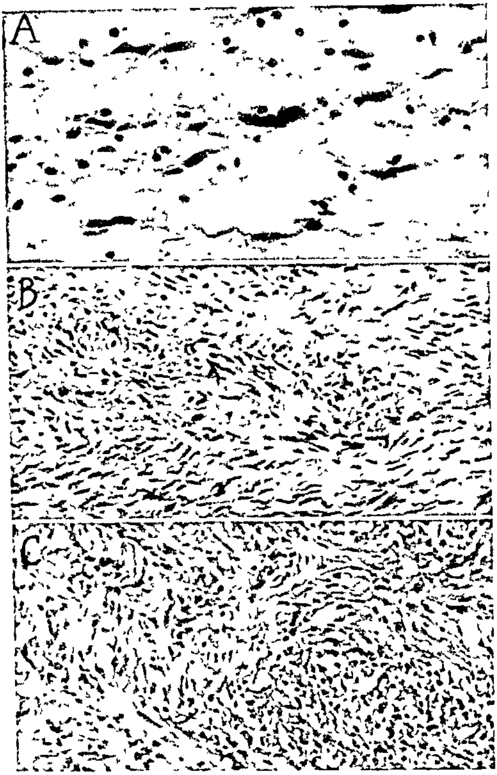

FIG. 5. *A*, case 1 High power, ×350. Dense fibrous-like tissue with elongated nuclei giving impression of palisading with loose connective tissue.

B and *C*, case 2 *B*, photomicrograph, ×250 showing nerve tissue. *C*, photomicrograph, ×250 Nodule from rib showing more active growth of nerve tissue but similar to original lesion.

A biopsy of the lesion on the rib was taken with the following report:

"The specimen consists of two pieces of firm, grayish-pink, gritty tissue each measuring approximately 1 cm. in diameter. Microscopic examination shows whorls of fibrous tissue arranged in irregular patterns. The nuclei of these fibroblasts vary greatly in size, shape and staining reaction and often are large, vesicular and with large nucleoli. A moderate number of mitotic figures are visualized. Diagnosis: Malignant schwannoma (Dr. Levin Waters)." See figure 5, *C*.

The patient expired on October 27, 1949.

PATHOLOGY

There are two types of schwannomas, the benign and the malignant schwannoma. Both of these types are associated with peripheral nerves and are extremely rare in the retroperitoneal space. The malignant schwannoma is often labelled a *fibrosarcoma, but the origin of this tumor is different.* In the main, the above two tumors arise from Schwann cells which have their embryonic origin, the neural crest. The Schwann cells are very active and multiply easily. Tissue cultures have shown that these cells can produce connective tissue fibers. Whenever a malignant tumor arises from the sheath of a peripheral nerve there crops up uncertainty in one's mind as to the embryonic origin of these cells. If this type of tumor arises from mesodermal connective tissue it is called a fibrosarcoma. It is uncertain whether or not the mesodermal element of a nerve sheath can produce a malignant fibrous tissue. The solitary, encapsulated, benign tumor which arises from the sheath of Schwann may be small, solid or large and cystic. The small tumors are solid, but as they grow larger degeneration occurs and cystic formation results. They grow slowly, usually without producing symptoms, although when a large nerve trunk is expanded, pain, paresthesia or other symptoms due to pressure may occur. The solid tumors are benign and are always encapsulated and rarely recur after surgical removal even if the capsule is left behind. It has been questionable whether or not a malignant tumor ever develops from them. Histologically, the microscopic picture is characteristic. Inside the sheath, the tumor tissue is composed of two parts. The cells of Schwann are arranged in twisted bands or cords accompanied by delicate connective tissue fibers. The cells may also be arranged so as to give the appearance of a tactile corpuscle, which is called a Verocay body. Del Rio Ortega, Penfield and Mason have divided the nerve tumors into two types, the fascialar and the reticular. The former consists of an orderly arrangement of parallel and intercellular fibers. The cells may also present transverse parallel ranks separated by nuclear free zones of densely aggregate fibers along with the terminal portions of the cells. The neuri*lemmoma consist of a form of reticular collogen* which, however, stains somewhat differently from the fibroblastic collogen. The reticular type shows a disorderly arrangement of a loose meshwork of cells of variable shapes with plentiful intercellular vacuoles or microcytes containing water or mucinoid fluid which stains bluish with benatoxylin. Regimented parallel fibers are not found and collogen fibers are scanty or absent in this type. The two types may be found together. Biologically, they grow slow and are encapsulated. If they are not entirely removed recurrence may develop.

COMMENT

These 2 cases of schwannomas occurred in young adult women and on the left sides. Both were operated upon successfully conserving the kidneys. One tumor was solid and relatively benign, and the other cystic and malignant. It is difficult to state how long these tumors had been present. The former had produced almost no symptoms while the latter had presented symptoms for 10 years. Schwannomas as a rule are relatively benign tumors, although the cystic ones may prove to be malignant. The former patient has remained well for two years, while the latter patient died of general metastatic lesions eighteen months from the time of the operation. Schwannomas are slow-growing tumors and rarely reach more than two centimeters in diameter. The schwannomas in the retroperitoneal space below the renal organ develop into large tumors which compress the ureter and influence its position and function. They are adherent to the posterior abdominal structures, both muscle and vascular tissues. Care should be taken to remove all of the tumor as in all tumor surgery. In the second case, it was more difficult to accomplish complete removal, and, as evidenced by its local recurrence, the tumor was not wholly removed. The widespread metastases indicate the true biological tendency in this one case of disseminating its growth to distant tissues. Neuropathological literature indicates that the tumors may become cystic and malignant, although on the whole they are considered relatively benign.

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PELVIOLITHOTRIPSY IN SURGICAL MANAGEMENT OF STAGHORN RENAL CALCULI

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Pelviolithotripsy as the term implies, refers to the fragmentation of the renal calculus through a pyelotomy incision. It is a definite adjunct in the surgical management of certain selected cases, particularly where there exists a low renal reserve, or in the solitary kidney, where nephrolithotomy would be hazardous. The concensus of opinion of such men as Zuckerkandl, Beer, Walters, and Counceller, Robinson, and Priestley favors pyelolithotomy over nephrolithotomy as the safer of the two procedures. The reports of Priestley and Dunn, and Prince, Scardino and Presti indicate that surgical removal of staghorn calculi is preferable to medical management.

In reviewing the literature we have not encountered an article that discusses fragmentation in detail. Simple fracture through the body of a staghorn calculus will often permit the atraumatic removal of the two fragments through a pyelotomy incision.

The Bigelow lithotrite was chosen because the blades are long and slender, and more easily introduced into the pelvis, and yet have great crushing power. The even, steady application of force obtained through the screw mechanism permits shearing the calculus into two major fragments without pulverizing it. The screw mechanism in contrast with the pistol grip type eliminates any sudden jerk at the time of fragmentation that would prove injurious to the kidney.

No attempt will be made to discuss the etiology; preoperative selection of cases for surgery; or postoperative medical management, as the literature is replete with excellent articles dealing with these subjects.

SURGICAL TECHNIQUE

The kidney, renal pelvis, and proximal ureter are completely mobilized by a combination of blunt and sharp dissection performed through an adequate lumbar incision. The posterior aspect of the pelvis is more completely visualized by elevating the renal hilum with vein retractors in the manner described by Walters, Counseller and Priestley. An elliptical incision (fig. 1, *A*) is then made in the renal pelvis extending from the superior to the inferior border on the posterior aspect with the convex curve directed toward the renal hilum. The posterior flap of renal pelvis is then peeled off the projecting pelvic portion of the staghorn calculus (fig. 1, *B*) and the pelvis is then gently retracted anteriorly. The calculus is then manipulated carefully and extracted if possible. In some instances because of close approximation of calculus to pelvis it is necessary to pass a curved hemostat around the pelvic portion of the calculus at the hilum in order to permit the introduction of the blades of the lithotrite. The female blade of the Bigelow lithotrite is introduced into the space between the anterior surface of the calculus and the pelvic mucosa; the male blade is then introduced

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on the posterior aspect (fig. 1, *C*). The most desirable plane for cracking the calculus as determined by preoperative x-ray studies is attained by gentle manipulation of the lithotrite. In the cases reported the calculus was sheared into two major fragments which were readily extracted through the pyelotomy incision. Small calculi may then be removed with stone forceps or scoop. In the presence of a dilated calyx with narrowed infundibulum the small calculi may be removed through a small, stab type nephrotomy incision as in case 2. Where a bulbous projection of the staghorn calculus is locked in a minor calyx it will be necessary to perform a small nephrotomy incision and fracture the calculus at the level of the constricted infundibulum. An x-ray study of the kidney is then made to determine if any radio-opaque calculi have been overlooked. The calyces are lavaged in an attempt to evacuate any nonradio-opaque calculi or debris that would act as a nidus for recurrent calculus formation.

An 18F bulb catheter, and two 5F ureteral catheters are introduced simultaneously into the renal pelvis through an inferior calyx (fig. 1, *D*). The balloon is distended with 3 cc of water, and left as a nephrostomy tube. The two ureteral catheters are advanced into the ureter 15 to 20 cm., and act as a splint. The elliptical pyelotomy incision is closed with interrupted 000 sutures of plain cat-

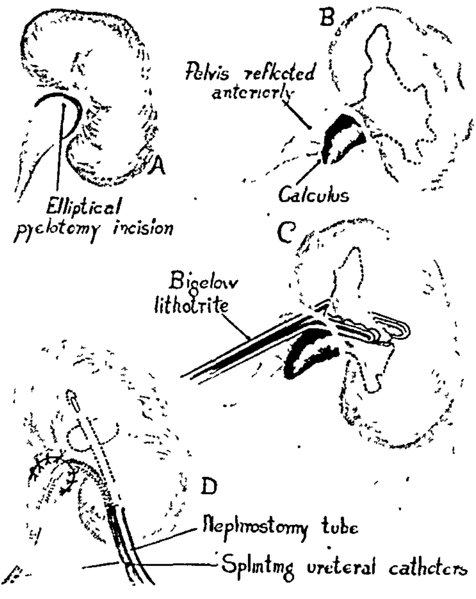
A
Elliptical pyelotomy incision
B
Pelvis reflected anteriorly
Calculus
C
Bigelow lithotrite
D
Nephrostomy tube
Splinting ureteral catheters

FIG. 1 Semidiagrammatic illustration of surgical technique. *A*, pyleotomy incision. *B*, reflection of pelvic flap. *C*, introduction of lithotrite. *D*, closure.

gut, no attempt being made to obtain a water tight closure. The kidney is suspended in favorable position beneath the twelfth rib, by Kelly triangular sutures. Gerota's fascia is approximated to the quadratus lumborum muscle with interrupted 00 chromic sutures in a modified type of Deming nephropexy. The region around the renal plevis is left open to permit favorable drainage. A Penrose drain is introduced into the parapelvic area posterior to the lower pole of the kidney, and a second drain along the mobilized portion of the ureter. The incision is closed in layers, and the nephrostomy and splinting ureteral catheters fixed to the skin with 0 silk sutures.

POSTOPERATIVE MANAGEMENT

The nephrostomy tube is irrigated only if definite impairment of drainage is evident. The balloon is decompressed in 48 hours. Solvent solutions are not used in the immediate postoperative phase, feeling that their irritant action outweighs their usefulness. Beginning at 72 hours the ureteral catheters are withdrawn 1 to 2 cm. daily. The Penrose drains are left undisturbed until there is a marked dimunition in drainage, then they are shortened daily. Ambulation is inaugurated on the fifth to seventh postoperative day, pelvic circulation having been stimulated previously by passive exercise of the lower extremities at frequent intervals.

The immediate medical management consists primarily of adequate supportive measures; hyaluronidase 150 TR units (Wydase) daily; and appropriate antibiotic therapy. The accepted methods for the prevention of recurrent calculus

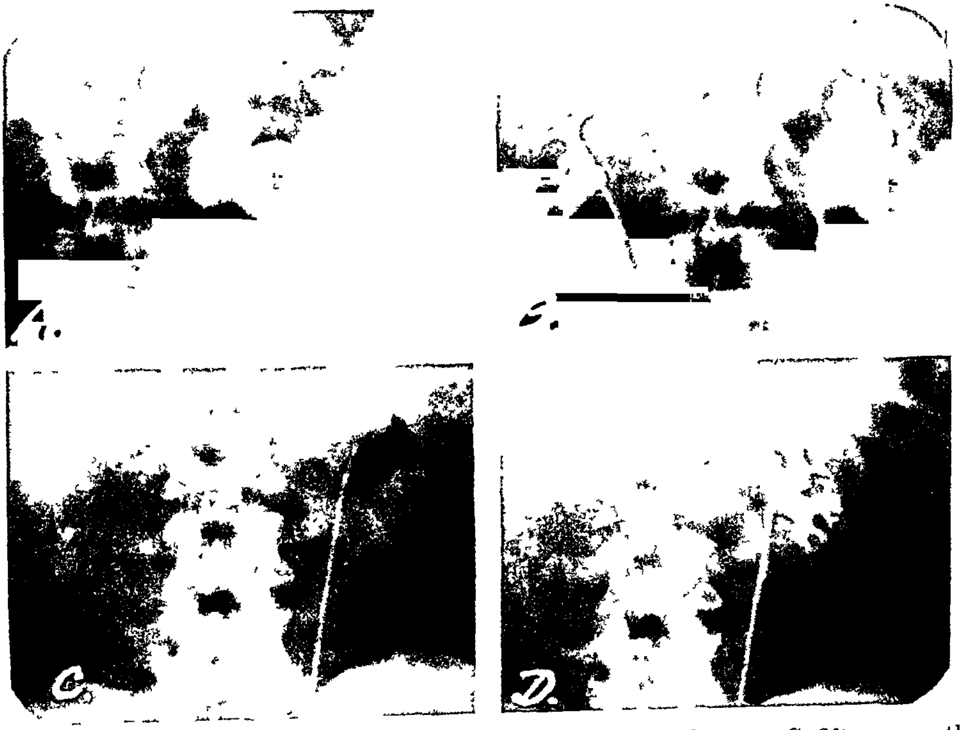

Fig. 2. Case 1. *A*, preoperative scout film. *B*, retrograde pyelogram *C*, fifteen months' postoperative scout film. *D*. retrograde urogram

formation are utilized after the patient has completed his postoperative convalescence.

CASE REPORTS

Case 1. Mr. F. L., aged 51, was seen because of two bouts of right flank discomfort. A scout film and retrograde urogram (fig. 2, *A* and *B*) revealed a small calculus lodged in an inferior minor calyx of the right kidney, and a left staghorn renal calculus. Indigo carmine appeared from the right kidney in 4 minutes, and from the left kidney in 10 minutes. Urine recovered from each kidney was sterile on culture, and blood chemistry studies were within normal limits. The right renal symptoms promptly subsided. The staghorn calculus was then removed in the manner described. The two major fragments (fig. 4, *A*) were easily extracted through the pyelotomy incision without evident trauma to the renal parenchyma.

Convalescence was uneventful. The voided urine has been sterile since the twenty second postoperative day. A scout film and retrograde urogram (fig. 2, *C* and *D*) made 15 months following surgery revealed no recurrent calculus formation, and an excellent return to normal of the calyceal system. The right renal calculus has remained stationary in size and asymptomatic.

Case 2. Mrs. K. R., aged 62, had a right nephrectomy performed 15 years previously for calculus pyonephrosis, at which time a small calculus was present in the left kdiney. In recent years she had noted mild, recurrent, left flank discomfort. The scout film and excretory urogram (fig. 3, *A* and *B*) revealed a large

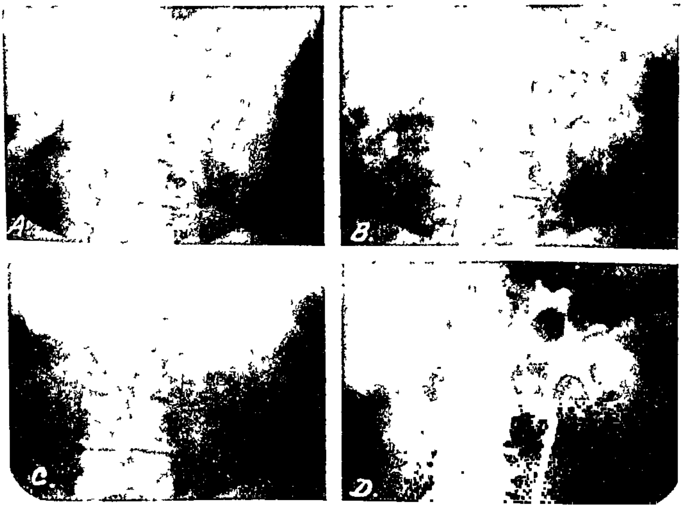

Fig. 3. Case 2. *A*, preliminary scout film. *B*, excretory urogram. *C*, three months' postoperative scout film. *D*, retrograde pyelogram.

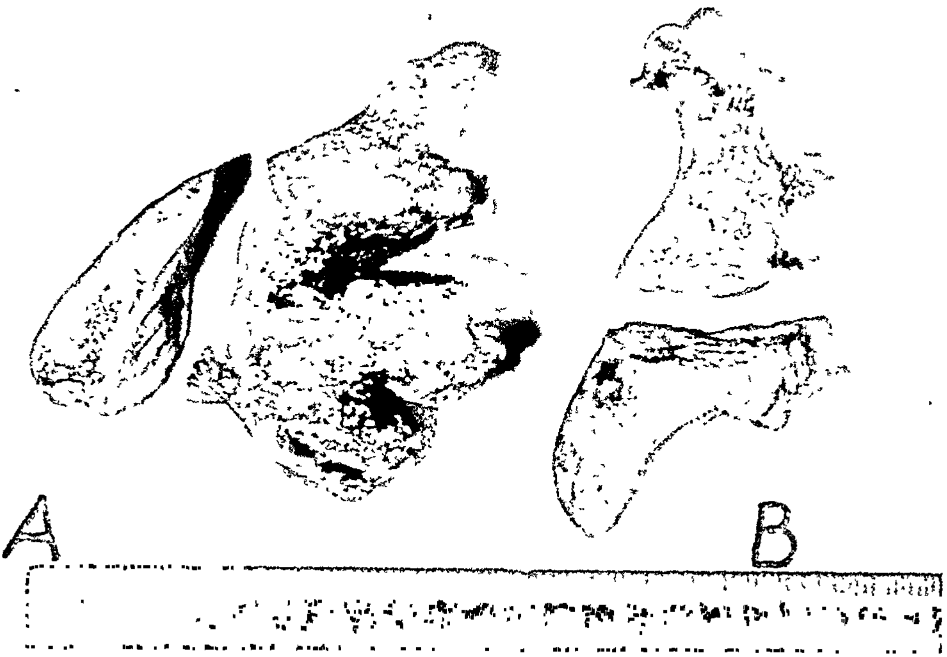

FIG. 4. Surgical specimens. *A*, case 1. *B*, case 2

staghorn calculus, and several smaller calculi in the solitary left kidney. The superior group of calyces appeared to be involved in a localized hydronephrotic change. The general condition of this patient was excellent; blood pressure 160 systolic and 90 diastolic; blood chemistry studies were within normal limits, and Gram's stain of the urinary sediment, negative for organisms.

At surgery the calculus was found to be in such close approximation with the pelvic mucosa that it was necessary to free it in the manner previously described, before the blades of the Bigelow lithotrite could be introduced. Figure 4, *B* shows the calculus sheared into two major fragments. Within 30 minutes following surgery the kidney was secreting relatively clear urine, and at no time was urinary suppression noted. The maximum elevation of nonprotein nitrogen was 42 mg. per cent.

Three months later the nonprotein nitrogen was 21.5 mg. per cent. The scout film and retrograde urogram (fig. 3, *C* and *D*) reveal no recurrent calculus formation, and a definite regression in the previously noted hydronephrotic changes. Repeated cultures of the urine have been sterile. The patient has been leading a fully active, comfortable existence.

DISCUSSION

Meticulous care in handling the kidney with low renal reserve during mobilization coupled with the atrumatic removal of the staghorn calculus tends to reduce to a minimum the likelihood of immediate postoperative urinary suppression. The use of the elliptical pyelotomy incision is very important. It permits the reflection of the pelvis and ureteropelvic junction out of the field of manipulation, and in contrast with the longitudinal pyelotomy incision there is no tendency for extension of the incision to involve the ureteropelvic junction with subsequent stricture formation This incision permits greater accessibility in manipulating the calculus, and thus facilitates the introduction of the blades of the lithotrite Due to the adequacy of the pyelotomy incision, digital palpation and instrumental removal of small calculi is simplified Closure is simple, and being located at the widest portion of the pelvis there is less likelihood of distortion by scar tissue

The shearing affect of the Bigelow lithotrite is evidenced by the surgical specimens (fig 4, *A* and *B*).

It is mandatory to correct any ureteropelvic junction obstruction at the time of surgical removal of the calculus

The two splinting ureteral catheters maintain the ureter and ureteropelvic junction in good alignment, and permit constant ureteral drainage of the renal pelvis The nephrostomy tube allows immediate drainage, and may be left in situ as a permanent method of drainage if the situation so demands Nephropexy, further enhances a favorable alignment of ureter and pelvis, and facilitates the change of nephrostomy tubes if this be necessary The parapelvic drains are left relatively undisturbed to prevent pooling of urine seeping from the pelvic incision, which would predispose for scar tissue formation and subsequent obstructive uropathy X-ray control at the time of surgery is of the utmost importance

The two cases reported fulfill the tenets laid down by Hess for obligatory, conservative renal surgery We believe that the favorable response to surgery in these two cases was due primarily to the relatively atraumatic method of removing the calculi

SUMMARY

The technique of pelviolithotripsy utilizing the Bigelow lithotrite is described and the use of this method of surgical management in selected cases of staghorn renal calculi advocated

The posterior elliptical pyelotomy incision is described and the many advantages of this incision discussed

Two cases of staghorn renal calculi requiring obligatory, conservative surgery are reported wherein this technique was utilized with favorable results

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SPONTANEOUS DISSOLUTION OF RENAL CALCULI

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Although rare, the spontaneous dissolution of renal calculi does occur. The literature on this subject was reviewed by Sisk and Bunts in 1935 and by Lassen in 1939. McCrea and Van Buskirk reported a single case in 1951. Despite these reports, the significance of this phenomenon seems to have been overlooked.

REVIEW OF LITERATURE

Scheele, in 1924, observed marked reduction in size of four renal calculi in a woman aged 34 over a period of 4 years. Hellström, in 1925, describing three patients, noted the spontaneous disappearance of a large recurrent calculus in the right kidney over a period of 5 years in a woman 24 years of age. A second and similar case was observed to occur over a 4-year period in a woman aged 26. Bilateral calculi were found to have disappeared in a man aged 45 over a period of 8 years. In this patient stones apparently developed during convalescence from a fractured femur. Hasselström reported almost complete disappearance over one month's time of a large renal calculus in a woman aged 40. This patient also suffered from a gastric ulcer. Nadeau, in 1934, reported the disappearance of several calculi in a solitary kidney over a period of 6 months. This patient was a nurse who drank a gallon of distilled water daily. Kearns, in 1935, reported the dissolution of a large renal calculus in a woman aged 42 over a period of several months. This patient disliked to drink liquids with the exception of beer. Barney reported the spontaneous dissolution of bilateral renal calculi in a male aged 22 over a period of about 3 months. The stones apparently developed during immobilization for fracture of the femur. Sisk and Bunts reported the complete dissolution of bilateral renal calculi in a female child aged 13 over a period of a few months. This patient had been ill with coxitis prior to discovery of her calculi. Lassen reported the disappearance of bilateral renal calculi in a woman aged 17 over a period of one year. This patient had been immobilized for disease of the hip joint prior to development of her stones. Wesson, in 1950, reported the case of a 21 year old male who was found to have bilateral renal calculi, one a staghorn, in the course of convalescence from a fractured femur. These stones underwent complete dissolution over a period of about 6 weeks. The patient was given an acid ash diet and ammonium chloride. McCrae and Van Buskirk, in 1951, reported one case of spontaneous dissolution of bilateral renal calculi which were apparently stones of recumbency. Gibson reported the following case in 1937. The patient, a man 48 years of age, came to the Southern Pacific Hospital suffering with renal colic. Urologic investigation revealed large bilateral renal calculi of the staghorn type associated with chronic pyrlonephritis. Since function was most impaired on the right, a nephrolithotomy was done on that side. The patient was then sent home to recuperate, with instructions to return

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within a month for operation on the left kidney. He did not return for 4 years. Investigation then showed that the large staghorn calculus in the left kidney had apparently disappeared spontaneously. The pyuria had likewise cleared up, and there was no evidence of recurrence on the right side. During these 4 years the patient had been under no dietary regimen or treatment of any kind. On his own initiative, he had for one year drunk a daily cup of tea brewed from horsetail grass.

CASE REPORTS

Case 1. In March 1951, a 75-year old man was admitted to the Stanford Service of the San Francisco Hospital with a complaint of prostatism. He was found to have an advanced carcinoma of the prostate and was placed upon stilbestrol by mouth. X-rays revealed the presence of an asymptomatic large left renal calculus. Because his general condition was poor, operation was not advised. Four months later, follow up x-rays disclosed the complete disappearance of the calculus. No treatment had been given for the calculus and the patient passed no stones. (See figure 1.)

Case 2 is reported through the courtesy of Dr. Emmett Henderson. A young woman, aged 23, was seen in May 1949. She complained of pain, of 1 week's duration, in the left renal area. She had previously been in good health. Excretory urograms disclosed a calculus obstructing the left ureteropelvic junction. The patient was advised to enter the hospital, but refused. She returned 1 month later at which time excretory urography showed no evidence of a calculus, and retrograde pyelograms were normal. No treatment had been given, and the patient had passed no calculi. (See figure 2.)

Case 3 is reported through the courtesy of Dr. Jack Lynn and Dr. R. H. Greeley. A 39 year old woman was first seen in April 1948 because of pain in the left renal area. She gave a past history of bilateral nephrolithotomy 4 years previously. Examination disclosed an acutely ill woman with tenderness over the

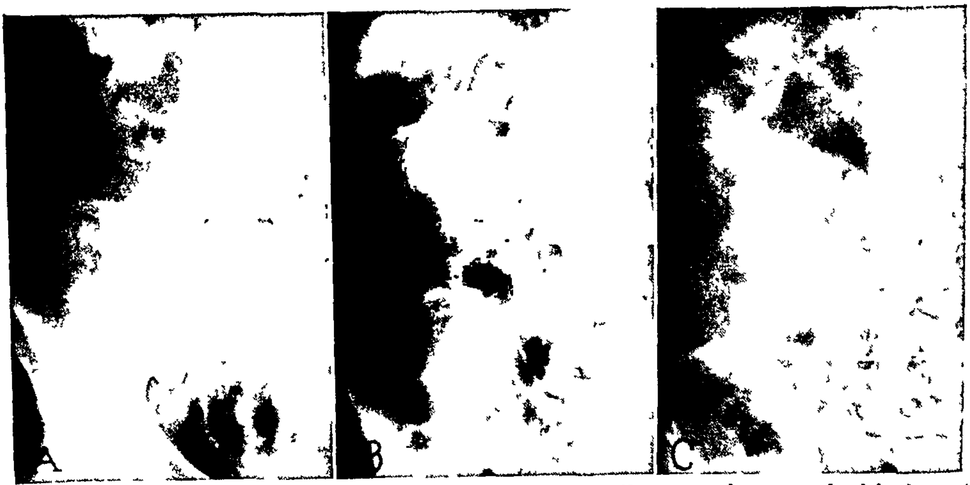

Fig. 1. Case 1. *A*, staghorn calculus in left kidney. (Film was photographed in inverted position showing calculus to be apparently in right kidney.) *B*, another view showing staghorn calculus in left kidney. *C*, film taken 4 months later showing disappearance of calculus.

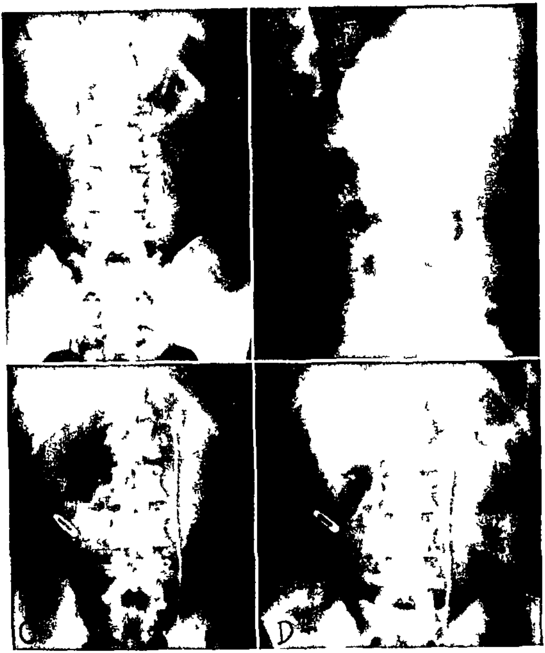

Fig 2 Case 2 *A*, excretory urogram showing calculus at left ureteropelvic junction, and suppression of function on left *B*, lateral view showing calculus *C* and *D*, films taken 1 month after *A* and *B* showing disappearance of calculus

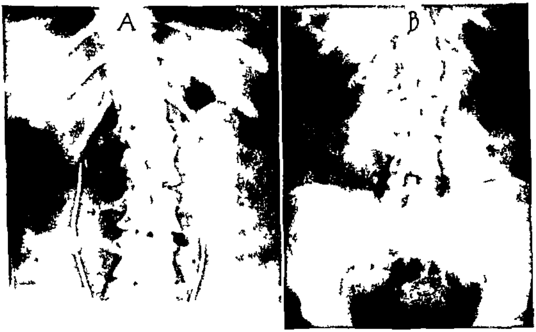

Fig 3 Case 3 *A*, plain film with catheters showing large calculi in lower pole of each kidney and calculus in upper left ureter adjacent to tip of catheter Calculus adjacent to catheter on right and superlateral to transverse process of left lumbar vertebra was in isolated calyx and not in pelvis or ureter *B*, film taken 8 months later showing almost complete disappearance of large calculi in both lower poles One calculus on right remains unchanged similar calculus persists on left side

left kidney, gross pyuria, and a nonprotein nitrogen of 103 mg. per cent. Retrograde pyelograms disclosed bilateral calculi in the lower pole of each kidney and a stone at the ureteropelvic junction of the left kidney. A diagnosis of chronic bilateral pyelonephritis was made and Pseudomonas aeruginosa was cultured from the urine. The patient was treated with antibiotics, a low phosphorus diet, and amphogel. Over a period of several months, the urine showed a pH of 6.0–6.5, a specific gravity of 1.002 to 1.010 with 2 plus albumin, and persistent pyuria. Eight months after her initial visit, x-ray examination disclosed an apparent disappearance of the calculus in the left uretero-pelvic junction, and marked diminution in size of the renal calculi in the lower pole of each kidney, only small fragments remaining. (See figure 3.)

Case 4. Although details of the case are unavailable, the late Dr. Clark Johnson observed a patient in whom a large staghorn calculus spontaneously decreased to about one-fourth its original size.

DISCUSSION

Although one of the reported cases was treated with a large water intake, one patient was given acidifying drugs and an acid ash diet, one patient drank large quantities of beer and little else, one patient was given stilbestrol, and one was given a low phosphorus diet and amphogel, none of these measures has consistently resulted in the successful planned dissolution of renal calculi. Until much more is known as to the mechanism of dissolution of calculi, the phenomena reported here must be considered as essentially spontaneous and due to unknown factors.

The fact that spontaneous dissolution can occur is of great significance in two respects: 1) It suggests that dissolution by medical treatment is a possibility. Additional knowledge of the physico-chemical factors involved in the formation and dissolution of calculi is needed before this can be accomplished. 2) It throws some additional light on the role of urinary colloids in relation to calculus disease.

Protective colloids in normal urine have been held responsible for keeping in suspension the sparingly soluble salts which constitute urinary calculi. The recent articles by Butt, et al., concerning the use of hyaluronidase make use of this theory as a basis for their claim of success in using this material to treat urolithiasis.

In view of the foregoing, it might be wise to consider some simple facts regarding the known physico-chemical activity of colloids.

The word "colloid" refers to a state of subdivision of matter and not a special kind of matter. In general, colloidal particles are larger than molecules but submicroscopic, ranging from one half micron to one millimicron in diameter. Ordinary suspensions settle out on standing, but colloidal suspensions remain suspended. The colloidal particles are sufficiently fine so that the Brownian movement overcomes the force of gravity. Thomas Graham, in 1862, observed that solutions of certain substances such as proteins, polysaccharoses, gums, etc., did not diffuse through parchment and other membranes as readily as sugars, salts, and other materials which crystallize. He called these substances colloids from the Greek word for glue. The crystalline substances which diffuse readily through membranes, he called crystalloids. We now know that many typical colloids such as certain proteins are crystallizable, while practically all crystalloids may, under proper conditions, be brought into the colloidal state.

The biologically important colloids are hydrophilic or "water-loving." That is, they have a great affinity for water and readily form stable solutions or gels. Examples of these are albumins, soaps, gums, tannins, starch, gelatins, glue, proteins, and complex carbohydrates. Suspensoids or lyophobic colloids include colloidal solutions formed by metals, inorganic salts, etc. There is no affinity between these particles and water. They are flocculated by very small quantities of electrolytes, and when so precipitated, cannot ordinarily be brought back into colloidal solution. The precipitation of suspensoids is therefore irreversible.

A "protective colloid" is one which will cause the finely divided particles of a suspensoid to remain in suspension whereas, in the absence of the protective colloid, the particles would settle out of the solution on standing. An example of this is the photographic dry plate. Silver chloride is formed from its ions in a solution containing gelatin. The gelatin coats each particle of silver chloride and prevents precipitation. Protective colloids will cause insoluble salts to remain in suspension but will not stop the formation of insoluble calcium oxalate and calcium phosphate, although it could hinder their precipitation and settling out of solution. Nor would the addition of a protective colloid cause a solid precipitate such as calcium oxalate or calcium phosphate to become resuspended.

From the foregoing, it would seem evident that although protective colloids may hinder the precipitation or settling out of insoluble salts in urine, they would not stop the formation of the insoluble salts from their ions or cause the solution of precipitates or solid calculi, unless they behave as crystalloids and *enter into actual chemical combination with the insoluble material.* Thus, it is apparent that protective colloids, as such, in urine could not be responsible for the spontaneous dissolution of urinary calculi.

The only rational explanation for the spontaneous dissolution of renal calculi is that a change in chemical equilibrium in the urine has occurred which favors solubility of the salts composing the stones. Whether this occurs in the case of calcium stones by 1) a decrease in the concentration of calcium, phosphate, carbonate, or oxalate ions in the urine, 2) by reduction of the pH of the urine, 3) by the increased excretion of substances forming soluble complexes with calcium, or 4) by any or all of the above plus the excretion of a catalyst to speed the reaction, is as yet unknown.

SUMMARY

Thirteen cases of spontaneous dissolution of renal calculi have been found in the literature. Three cases are reported here and one other case is known to have occurred. Of all these cases, five were apparently stones of recumbency, and two patients suffered from chronic pyelonephritis. It seems likely that spontaneous dissolution of renal calculi occurs more commonly than one might suspect from the literature.

Spontaneous dissolution of renal calculi is significant because 1) it suggests that the medical dissolution of calculi may be a possibility, with increased knowledge and 2) this phenomenon can be explained only on the basis of a change in chemical equilibrium in the urine favoring solubility of the salts composing the calculus, and 3) an increase in protective colloidal material in urine will not alone cause the dissolution of renal calculi.

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CLINICAL MANAGEMENT OF RENAL LITHIASIS WITH HYALURONIDASE

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This presentation is an analysis of the clinical results obtained by using hyaluronidase for control of renal calculus formation in 36 patients Particular emphasis is directed toward indications for hyaluronidase therapy, determination of proper dosage, and contra-indications to usage of this drug The physicochemical mechanism by which parenteral administration of hyaluronidase increases the protective urinary colloids and aids in the prevention of renal calculi has been reviewed previously[1-7]

Clinical, laboratory, and x-ray procedures usually employed for investigating patients with stones are carried out, with the exception that cystoscopic examinations and retrograde pyelo-ureterograms are not performed if it is possible to obtain all necessary information without these measures Bleeding or exudate formation may nullify the accuracy of the protective urinary colloid determinations Excretory radiographic studies are routinely made when renal function is adequate

The effect of hyaluronidase on urine may be conveniently followed in a series of uncentrifuged specimens, taken before and during hyaluronidase therapy, and allowed to settle for one hour at room temperature[1] In such a series, the turbidity and sediment usually begin to diminish in specimens voided about 30 minutes after the injection When turbidity increases in successive 1 hour specimens, another dose of hyaluronidase is needed If no decrease in turbidity and sediment is observed, the dose of the enzyme should be increased As a supplement to this testing procedure, the response may also be studied by comparing the rate of formation of deposits on the glass connecting tip attached to indwelling catheters during alternate periods with and without hyaluronidase injections This effect is most pronounced in nephrostomy drainage tubes and least in bladder catheters with intermediate effectiveness in ureterostomy catheters

Reduction in surface tension of urine closely correlates the clearing of tur-

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[1] Butt A J, Hauser, E A and Seifter, J Effect of hyaluronidase on urine and its possible significance in renal lithiasis J A M A 150 1096-1098, 1952

[2] Butt A J, Hauser, E A and Seifter, J Effect of hyaluronidase on protective urinary colloids and its significance in treatment of renal lithiasis New Orleans Med & Surg J 104 754-758 1952

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bidity and sediment if these are present initially. Tensiometric determinations are of greatest value when the urine is initially clear with no sedimentation. We have found that the average surface tension of urine in white males and females is 65 and 60 dynes per centimeter respectively.[5, 8] Following injection of sufficient dosage of hyaluronidase, the surface tension decreases from 8 to 14 dynes per centimeter within 30 minutes to 2 hours and remains decreased as long as the effect of hyaluronidase is being maintained.

The lyophilized hyaluronidase is reconstituted with sterile saline rather than with distilled water. To the vial containing 1500 turbidity reducing units (T. R. units), 10 cc or 5 cc of saline are added with aseptic precautions to provide a solution containing 150 or 300 T. R. units per cubic centimeter respectively. The latter concentration is convenient when the larger doses are required. When prepared with strict aseptic precaution, such solutions are stable without refrigeration for 2 weeks. If the hyaluronidase is in standardizing units, other than turbidity reducing units, their relation to the other must be determined. For example, 500 viscosity units are approximately equivalent to 150 turbidity reducing units. In all cases, the subcutaneous injection site should be rotated. If local infection develops, as in patients instructed to use hyaluronidase at home between office visits, the infected site should be avoided. Needles of 25 G and ⅜ inch are recommended.

Observations to date indicate that patients vary widely in the quantity of hyaluronidase required to clarify pathologic cloudy urines, and the dosage must therefore be determined individually. In approximately 80 per cent of the cases, clarification of the urine occurs after subcutaneous doses of 300 to 600 turbidity reducing units of hyaluronidase. The urine response to suitable doses of hyaluronidase is rapid and easily ascertained. This usually occurs within 30 minutes to 2 hours after injection. The dosage requirements are greater in the presence of infections, such as those due to P. aeruginosa and streptococci, or to urea-splitting organisms, particularly staphylococcus or Proteus. In such cases, dosages as high as 900 to 1800 T. R. units every 24 hours may be indicated. Also "split" dosages, i.e., 600 to 900 T. R. units every 12 hours may be necessary to keep the urine free of sediment.

Contra-indications to hyaluronidase therapy are hypersensitivity to the drug and impaired renal function. The highly purified enzyme used in our studies has little tendency to produce allergic reactions. In over 900 of our patients who have received injections of hyaluronidase, only three had significant localized urticaria and 2 of these were later treated without reaction. In one of the patients a different brand of hyaluronidase was administered and no reaction occurred. Desensitization to the drug has not been attempted since the injections can usually be resumed without further sensitivity response after a rest period. Also we have observed that inadequate dosage of hyaluronidase may be dangerous, due to the fact that "sensitization" of urinary crystals may occur with acceleration of stone growth. If clarification of the urine does not develop within 6 to 8 hours on the dosage outlined above, the treatment should be discontinued.

[8] Andreas, J. M., Hauser, E. A. and Tucker, W. B.: Boundary tension by pendant drop. J. Phys. Chem., **42**: 1001–1019, 1938.

The treatment of severe calculus disease by hyaluronidase demands day to day control. The management should be carried out considering stone as a constitutional as well as a local disease. Hyaluronidase therapy should be considered adjunctive, as all other forms of treatment usually employed are instituted. Metabolic disorders are corrected, if possible. Antimicrobial drugs and urologic measures are employed according to usual indications. If the stone is phosphatic, we prescribe Basaljel, two tablespoonsful after meals and at bedtime. This dosage is well tolerated and causes a reduction in urinary phosphate excretion. Appropriate dietary measures are instituted and large doses of vitamin A are prescribed in all stone cases.[7] Each patient is urged to maintain a daily urine output of approximately 3000 cc. In short, every measure is utilized which promises to assist in minimizing formation, growth or recurrence of stone.

During the past 30 months, we have observed 311 patients with renal lithiasis. Of this number, 54 were selected for hyaluronidase therapy because they showed a marked tendency to formation of renal calculi and because conditions were favorable to enhance the rate of stone growth. The cases of patients who had followed the regimen for less than 20 months were excluded from this series, as they would not seem to provide a substantial test of therapeutic efficacy. Thirty-six of the 54 patients have been on hyaluronidase therapy for periods ranging from 20 to 30 months, average 23 months. In these patients, no previous forms of therapy had been effective in reducing formation or growth of stones. Twenty of the patients had previously undergone one or more operations for stone, nine of which were nephrectomies. Ages ranged from 13 months to 78 years. There were 20 males and 16 females. All of the patients were white.

For control, the clinical course of the 36 patients before institution of hyaluronidase therapy was used. We fully realize that this did not provide a completely reliable basis for comparison. Estimation of the time interval between the first knowledge of presence of stone and institution of therapy was often difficult and possibly inaccurate. Chemotherapeutic and antibiotic preparations were fewer and less readily available during the pre-treatment (control) period, although in most cases sulfonamides and penicillin had been used. Some had received streptomycin, aureomycin, terramycin and chloramphenicol. All of the selected 36 patients followed the therapy reasonably well, although the regimen was not strictly adhered to in every case and deviations were demonstrable on an objective basis. In fact, some deletions of therapy provided the most impressive exhibition of the effectiveness of the program. Three patients discontinued the drug for periods of 8 weeks, 9 weeks and 17 weeks respectively. In these patients, stone formation had been controlled while taking hyaluronidase and after discontinuing the drug there was rapid increase in size of existing stones.

As a result of our earlier observations concerning the responsiveness of certain types of renal calculus formation to hyaluronidase therapy, the 36 patients in this series were classified into group A and group B. Group A included 15 patients with multiple, small, calyceal or other small calculi, rapidly forming in a solitary kidney or in both kidneys. From the case histories, laboratory and x-ray findings, these were considered to be primary stones which we now believe to be caused by innate or acquired deficiency of protective urinary colloid. Group B included 21

TABLE 1. *Summary of results following administration of hyaluronidase for renal lithiasis*

GROUP	STONE FORMATION CONTROLLED	STONE FORMATION SLOWED	STONES SMALLER AND LESS DENSE	STONE FORMATION NOT CONTROLLED
A—15 cases	9 (60.00%)	3 (20.00%)	1 (6.67%)	2 (13.33%)
B—21 cases	7 (33.33%)	7 (33.33%)	1 (4.77%)	6 (28.57%)

patients with large stones or large and small stones in a solitary kidney or in both kidneys. These were considered to be secondary type stones or secondary stones superimposed on an original primary stone as a nucleus. These stones resulted from stasis and infection, hyperexcretion of crystalloids, recumbency, hyperchloremic acidosis, or other known factors.

Results (table 1) were graded: 1) control of formation or growth of stone and no passage of stone; 2) reduction in rate of development and growth of stone as compared to previous calculogenesis; 3) diminution in size and density of stones; 4) failure to arrest or retard development and growth or passage of stone. Roentgenograms were made every 60 to 90 days on all patients in this series.

Group A: In 11 of the 15 patients, stones were available for analysis. Nine were composed of calcium oxalate or calcium oxalate and apatite and one each of cystine and uric acid. The last two named types of stone were not demonstrated by x-ray, but cystine and uric acid calculi were frequently passed and recovered for analysis. Urine culture was negative for growth in 13 of the patients; B. coli was present in one; Staphylococcus aureus, non-urea splitting, was present in one. Patients in group A generally required smaller doses of hyaluronidase than those in group B. Three required 150 T. R. units every 24 to 48 hours; 9 required 300 T. R. units every 24 hours; 3 required 600 T. R. units daily.

Group B: In 7 of the 21 patients, stones were available for analysis. Five were composed of apatite and ammonium magnesium phosphate, one of apatite and calcium carbonate, and one of cystine. Urine culture was positive for growth in all of these patients. Five patients had infection due to B. proteus; 5 with urea splitting Staphylococcus aureus; 3 with P. aeruginosa; 1 with B. coli, and 7 with mixed infections, non-urea splitting. One patient had clinical, laboratory and x-ray evidence of hyperparathyroidism but had refused operative exploration of the neck. Twelve patients in group B required 300 T. R. units daily; 7 required 600 T. R. units daily; 1 required 900 T. R. units daily, 600 in the morning and 300 at night; 1 patient required 900 T. R. units twice daily.

In group B, 2 patients had acceleration of development and growth and passage of stone resulting from sensitization of urinary crystalloids, due to too small amounts of hyaluronidase being administered. One of the failures was a patient with nephrocalcinosis due to renal acidosis. In our experience, hyaluronidase therapy has been relatively ineffective in treatment of 5 of 6 cases of bladder stones. Vesical calculus formation was controlled in a 90 year old man who had previously formed many stones following recumbency as a result of a hip fracture.

An additional 18 patients have received hyaluronidase preoperatively and postoperatively where renal surgery required catheter drainage. In 12 of these, the catheters were maintained free of calcareous deposits. Two paraplegics, not included in these series, should be mentioned. One patient had poliomyelitis and the other was paralyzed following traumatic section of the cord at the level of the sixth thoracic vertebra. Both of these patients had rapidly formed renal calculi soon after becoming recumbent. Hyaluronidase therapy was effective in preventing formation of new stone and growth of existing calculi over a period of 16 months.

There is evidence from preliminary studies that hyaluronidase therapy enhances antibacterial effectiveness of chemotherapeutic and antibiotic agents. This effect is presumably due to dispersing and peptizing action of the increased amounts of protective colloids.

DISCUSSION

Any physician's office or laboratory can make the necessary determinations of the effectiveness of hyaluronidase on clearing of urine. Patients are instructed to self-administer hyaluronidase and control the dosage by observing the urine in the same manner as the diabetic learns to take insulin and test his urine. We arbitrarily attempt to keep the urine clear for 16 to 24 hours following one injection. Occasionally injections must be given twice daily. This is especially so in postoperative or paraplegic patients. The question as to when it is safe to discontinue the therapy cannot be answered at this time. We suspect that patients who tend to form stones readily may have to remain on the regimen indefinitely. Prolonged usage of hyaluronidase therapy has produced no recognizable histopathologic lesions or significant adverse metabolic effects. The long continued application of any program requiring the consistent co-operation of the patient presents certain problems. Some patients tire of daily injections of a drug; and over a period of months, expense to the patient may be a significant factor.

It is most helpful to take the time to be explicit to the patient concerning the nature of his difficulties, to show him his x-rays and to point out to him any change or absence of change in size and number of stones which occurs during the course of therapy. In so doing, the patient becomes more conscientious in following directions and more faithful in closely adhering to the regimen with follow-up care. Finally, he becomes more understanding and co-operative when it appears that stone formation and development is being controlled in his case. The physician's interest and willingness to explain to the patient his problem of renal calculus disease and the objectives of the treatment go far in increasing the possibility of a favorable final result.

SUMMARY AND CONCLUSIONS

Hyaluronidase therapy is an effective adjunctive measure in the control of renal calculus disease. The dosage of hyaluronidase must be determined individually. No severe adverse side effects have been noted when hyaluronidase was properly administered.

The effect of hyaluronidase has been found to be most useful in management of primary, multiple, rapidly recurring, small calyceal stones. Even with the administration of larger doses of hyaluronidase it is less effective in the treatment of secondary calculi. Hyaluronidase therapy is also effective in renal surgery requiring drainage and in renal calculus conditions which present surgical hazards.

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MANAGEMENT OF URETERAL CALCULI

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Certain cases of ureteral calculi are complicated by the presence of one or more factors which dictate choice of treatment and therefore present no therapeutic problem. Among these are patients with stones lodged in the upper or middle third of the ureter, where manipulation is impractical because of their position. If, because of their size, the stones cannot be expected to pass spontaneously, or if they are producing partial or complete obstruction, surgical removal is obviously indicated. Small nonobstructive stones in these areas, on the other hand, may be treated expectantly. It is therefore usually only those stones in the pelvic or intramural portions of the ureter which test the urologist's judgment as to the proper plan of treatment. Calculi obviously too large to pass, those causing considerable dilatation above with renal damage, those associated with severe infection, those producing acute obstruction which cannot be relieved by passage of a ureteral catheter and those in which function of the opposite kidney is also compromised actually present little or no problem, since ureterolithotomy is usually indicated. It is, however, those stones measuring less than ¾ cm. in diameter producing relatively little or no obstruction or renal damage, usually without infection, in which there is a possibility of either spontaneous or manipulative passage, that one must select the plan of treatment which will be least dangerous to the patient and most certain of recovery of the stone, and will entail the shortest hospital stay.

It is, of course, axiomatic that once mechanical intervention is initiated, it must always be followed through until ultimate recovery of the stone, since the effects of instrumental infection, trauma and congestion with resultant obstruction make it practically impossible to terminate any program of mechanical intervention short of recovery of the stone, without the inevitable consequences of renal obstruction, infection, loss of function and perhaps loss of the kidney. With this uppermost in mind, it becomes the obligation of the urologist to decide which of the various methods offers the best chance of recovery of the stone with the shortest morbidity, the least risk and the greatest assurance of preservation of renal function. Among the factors to be considered are the age of the patient, the status of the opposite kidney as well as the one involved, the presence or absence of infection, the size and multiplicity of the stones, the general health of the patient and his financial status. Obviously, operative cystoscopy, when feasible and when it offers a reasonable chance of recovery of the stone, should be the procedure of choice as it entails shorter hospitalization and lower morbidity. Our experience indicates that it is preferable to confine such treatment to use of multiple catheter dilation of the lower segment of the ureter over a period of several days, whenever possible to introduce such catheters, or use of the

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TABLE 1. *Ureteral stone distribution*

SITE	STONES	%
Lower	200	73
Middle	23	8
Upper	51	19
Total	274	100

Johnson wire basket. Occasionally, it has seemed desirable to employ first one and then the other, and in some instances repeated manipulations, provided the patient's general condition as well as the status of the kidney warrant such practice. In other instances, in which the size of the stone, relative loss of function of the involved kidney, presence of severe infection, or status of the opposite kidney suggest that the risks and uncertainties of operative cystoscopy are unjustifiable, we do not hesitate to perform ureterolithotomy immediately, both to protect the patient's renal function as well as to offer the one sure means of removal of the stone. There are always instances, however, in which use of multiple, conservative cystoscopic procedures fails to recover the stone and results in a longer morbidity with ultimate open ureterolithotomy and occasionally some loss of renal function or even loss of the kidney. The ever present possibility of such an outcome has therefore prompted us to compare our results in the management of ureteral stones treated by the various alternative courses.

We have reviewed the records of 274 selected patients with ureteral calculi treated at the Ochsner Clinic during the past ten years. Only those patients whose courses were followed to their ultimate conclusion were included.

Table 1 shows the distribution of the calculi according to site in the ureter. Three per cent of the entire series were bilateral and 9 per cent were multiple.

UPPER URETER

Ninety-four per cent of the 51 stones located in the upper third of the ureter were producing obstruction, 75 per cent of which were more than ¾ cm. in diameter. Twenty-three were associated with infection. Eighty-two per cent of this group were removed surgically and 6 (12 per cent) were subjected to nephrectomy because of complete loss of renal function when first seen. Their average hospital stay was 12 days. Only 3 (6 per cent) were passed spontaneously.

MIDDLE URETER

All 23 stones located in the middle third of the ureter were obstructive and 90 per cent were more than ¾ cm. in diameter. None passed spontaneously. Nineteen (83 per cent) were removed surgically and the remainder (17 per cent) were subjected to primary nephrectomy because of complete loss of renal function when first seen. Their average hospital stay was 11 days.

As can be seen from these statistics, primary ureterolithotomy is usually the procedure of choice in upper or midureteral stones since most of these are large and obstructive. The duration of hospitalization is short and the morbidity is low.

TABLE 2. *Operative cystoscopy*

SIZE	OBSTRUCTIVE		NONOBSTRUCTIVE	
	Cases	%	Cases	%
Under ¾ cm.	49	65	13	17
Over ¾ cm.	10	13	4	5

TABLE 3 *Operative cystoscopy, lower ureter*

	CASES	%	AVER. HOSP. (DAYS)
Successful initial manipulation	34	45	4
Multiple catheters, initial success	14	18	7
Manipulation with extraction by multiple catheters afterward	7	9	9
Spontaneous passage after manipulation	6	8	9
Spontaneous passage after catheters	2	3	8
Ureterolithotomy after manipulation	10	13	25

LOWER URETER

In 81 (41 per cent) of the 200 patients with stones located in the lower third of the ureter the stones passed spontaneously. In none of these was there significant obstruction or renal damage. In only 7 of the 81 stones passed spontaneously was the diameter more than ¾ cm. All these patients were readily accessible to us for continued observation and care, when necessary, so that expectant treatment was possible in this group. In the remaining 59 per cent of cases, because spontaneous passage was considered highly improbable, some form of manipulative or operative intervention was indicated.

Seventy-six (38 per cent) were subjected to operative cystoscopy (table 2). In 82 per cent of these the stones were under ¾ cm. in diameter; 65 per cent were obstructive and 17 per cent nonobstructive. Eighteen per cent were over ¾ cm. in diameter; 13 per cent were obstructive and 5 per cent nonobstructive. Ninety-

TABLE 4. *Lower ureterolithotomy*

TYPE	CASES	%	AVER HOSP (DAYS)
Primary	32	76	15
After op. cystoscopy	10	24	25
Total	42		

TABLE 5. *Nephrectomy*

TYPE	CASES	AVER HOSP. (DAYS)
Primary	10	13
Secondary	2	35
Total	12 (12.5%)	

four per cent of the stones successfully recovered were less than ¾ cm in diameter

As can be seen in table 3, thirty-four stones were recovered by initial basket manipulation with an average hospital stay of 4 days, 14 passed immediately after initial multiple catheter dilations with an average hospital stay of 7 days, 7 passed immediately after multiple catheter dilations following failure of basket manipulation with an average hospital stay of 9 days Eight stones passed later after manipulation or catheter dilation, with an average hospital stay of 9 days Ten patients were subjected to secondary ureterolithotomy following unsuccessful operative cystoscopy with an average hospital stay of 25 days, in 9 of these the stones were over ¾ cm in diameter and obstructive This represented 65 per cent of the stones of this size wherein manipulation had been attempted

Thirty-two (21 per cent) of the lower ureteral stones were treated by primary ureterolithotomy with an average hospital stay of 15 days and no complications (table 4) Thirty-one of these were over ¾ cm in diameter, only 6 of which were nonobstructive Only one of the stones was under ¾ cm in diameter but it was obstructive The average hospital stay in this group was 15 days

Three of the 9 patients with bilateral calculi were treated by bilateral ureterolithotomy In one patient unilateral ureterolithotomy was done and the opposite side treated expectantly Primary nephrectomy was performed in 10 patients because of loss of renal function when first seen (table 5)

The complications in general were those of urinary sepsis This was adequately controlled by free urinary drainage and chemotherapy in most instances Secondary nephrectomy was required in 2 cases One resulted from a cortical abscess following operative cystoscopy Irreparable ureteral damage and infection following manipulation and attempted ureterolithotomy necessitated nephrectomy in the other

There was one recognized case of ureteral perforation following operative cystoscopy which was drained surgically The filiform tip of the stone basket disengaged in the ureter in one case necessitating ureterolithotomy and removal of the tip Injury to the internal iliac vein required ligation of the vessel in one case of lower ureterolithotomy

In the entire series there were two deaths in the immediate postoperative period, a mortality rate of 0 7 per cent One resulted from renal failure and the other from generalized tuberculosis

CONCLUSIONS

✓Stones in the upper and middle thirds of the ureter should be subjected to primary ureterolithotomy unless spontaneous passage seems probable

Large stones in the lower third of the ureter are best handled by primary ureterolithotomy Most manipulative failures in this series occurred in patients with stones over ¾ cm in diameter

When initial manipulation fails, subsequent manipulations are also unsuccessful in a high percentage of cases and result in a significant increase in morbidity, complications and duration of hospitalization Ureterolithotomy is, therefore, usually indicated after manipulative failure unless spontaneous passage seems imminent

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REMOVAL OF URETERAL CALCULUS BY A NEW CATHETER TYPE EXTRACTOR

THOMAS A. DAVIS

Many times I have wished, on passing a catheter by a ureteral calculus, that by some immediate conversion of the catheter, it would become a snaring or grasping instrument. After much thought and experimentation and trial, a device was evolved with which I have removed ureteral calculi, on the first attempt, in four consecutive cases.

The instrument was constructed by passing an S.F. 00 nylon thread through a transverse hole in the ureteral catheter at the 10 cm. mark, and passing each end of the thread into the lumen through separate holes on opposite sides of the catheter at the 15 cm. mark and then down through the lumen until it exits from the outer or butt end. A convenient length of thread is that which will permit about 5 cm. of each end to extend beyond the butt end of the catheter. The nylon thread must be single filament type, because braided is not stiff enough to thread down the lumen. The holes were made by simple needle puncture. A No. 24 hypodermic needle is the right size for making holes for No. 00 nylon S.F. thread (fig. 1). The hole nearest the tip of the catheter must be far enough from the tip so that the tip end of the catheter will not be bent or looped over when traction is exerted on the threads. In making the anchor holes at the tip end of the working segment, the needle may be passed obliquely through the catheter, thus creating a hole in opposite sides of the catheter, but at about 3 mm. different levels from each other. This practically eliminates any weakening of the catheter by the holes.

If the calculus is not too high in the ureter to make it impossible, the segment of catheter above the anchor hole of the thread should be long enough that successive sweeps of the instrument may be made, if necessary, to snare the calculus, without the catheter being withdrawn completely past the calculus. A stylet may be inserted the full length of the catheter lumen with the threads in place. The catheter which I used was of 6 caliber with an olive tip.

Extraction catheters were made by conversion of catheters of other calibers and types of tips with appropriate size of thread and stylets. I use S.F. 00 nylon for No. 6, 000 for No. 5, and 0000 for No. 4 catheters. A stylet slightly smaller in caliber than usually used for a given sized catheter with the end, which is inserted up the catheter, snipped at a rather sharp angle, is more readily inserted in the catheter than the usually furnished stylet with the catheters of a given size. The threads in the catheter do not prevent fluid from being able to pass through it, and it can be used as a catheter to drain the ureter, or to instil lubricant or contrast media into the ureter. Furthermore, sterilizing solution forced in at the butt end will exit at the tip openings, passing the entire length of the lumen. Withdrawal of the threads, exiting from the lumen at the butt end will cause a curving or looping of a segment of the catheter, and with the segment of

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the threads outside of the lumen at that level, will form a complete loop. Withdrawal of the instrument from a ureter with the loop formed above a calculus may serve the purpose of snaring the calculus and removing it, or of dilating the ureter. Once the calculus is well engaged, traction may be temporarily completely released on the threads so as to enable removal of the cystoscope, then reapplied without disengaging the calculus.

The loop can be formed, collapsed, and re-formed within the ureter at any level, at the will of the operator. The size of the loop is controllable within the limits imposed by the distensibility of the ureter, and not dependent upon an uncontrollable balance between elasticity of the instrument and constrictive power of the ureter.

The angulation or looping of the catheter can be done with the stylet in place. A novel feature is, that with a 5 cm. working segment, a 1 cm. withdrawal of the ✓ threads will produce a loop of approximately one cm. transverse opening. As with any instrument, good judgment and proper technique are necessary, and the size of the loop formed should be in proper relation to the size of the calculus and the diameter of the ureter. A ureter that will admit an 18F circular bulb, will contain without additional stretching, approximately a 1 cm. width loop of this instrument.

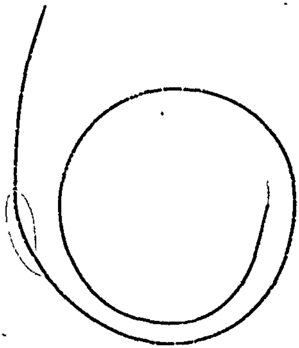

FIG. 1. Photograph of ureteral calculus extractor catheter

✓This calculus extractor can be inserted to any level of the ureter with the simplicity, facility and safety equal to that of an ordinary ureteral catheter of similar size and style. If for some reason, after having snared a calculus in the ureter, it is desired to release the calculus and withdraw the extraction catheter, it may be done following release of traction on the threads, unless, perhaps, there is a complete loop of the catheter part of the instrument around the calculus. By releasing one end of the thread and pulling on the other end, the entire thread may be removed with the catheter in the ureter, thus converting the extractor to an ordinary catheter, except for the remaining thread holes.✗

✓In the case considered suitable for the use of this instrument, it was cystoscopically inserted up the affected ureter to a distance sufficient to place the loop

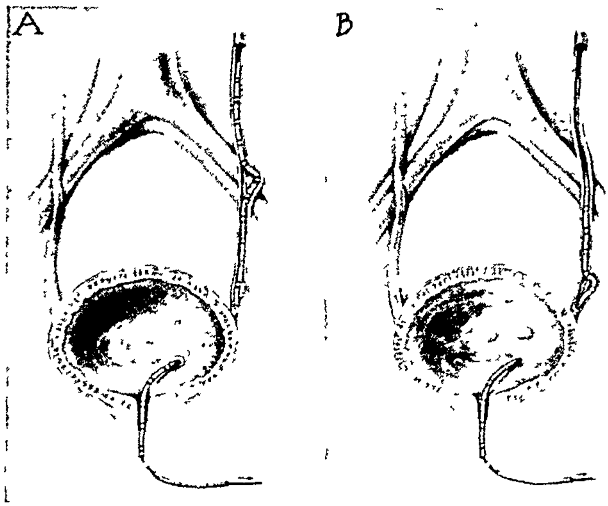

FIG. 2. *A*, loop forming due to traction applied to threads as they emerge from catheter. *B*, stone engaged in loop of catheter.

segment above the calculus, with the stylet in the catheter. The stylet was then withdrawn. The loop was formed (fig. 2, *A*) by withdrawing the threads about 1 to 2 cm. or until a marked resistance to further withdrawal of the threads was encountered. A small hemostat or needle holder with thin rubber covered jaws is convenient for grasping the threads. With the threads in place, either manually, or by clamping adjacent to the butt end of the catheter with a hemostat, and with the other hand manipulating the cystoscope, the catheter was slowly withdrawn with the ureteral orifice under observation. When the loop engaged the calculus, an immediate marked resistance was encountered to further withdrawal of the instrument (fig. 2, *B*). The traction on the threads was then partially released. Combined traction was then made on the threads and catheter to remove the calculus. If the loop should exit from the ureteral orifice without the calculus, it can be collapsed by releasing all tension on the threads and the catheter rotated 90 degrees and re-inserted up the ureter for another attempt to remove the calculus.

The dilatation of the ureter resulting from withdrawl of the formed loop would be advantageous. The instrument can be used as a ureteral dilator when such treatment only is desired. Dilatation of localized segments of the ureter may be done, also. The following 2 cases of which illustrative x-ray films are existant, show the actual use of the instrument.

CASE REPORTS

Case of M. J. Small calculus in lower end of left ureter. Under spinal anesthesia, February 20, 1953, the calculus extractor catheter was passed up the left ureter cystoscopically to the 20 cm. mark. The loop was formed (fig. 3), and the instrument withdrawn. The calculus was engaged and pulled into the bladder, remaining in the loop, and was removed from the bladder with removal of the cystoscope and extractor catheter.

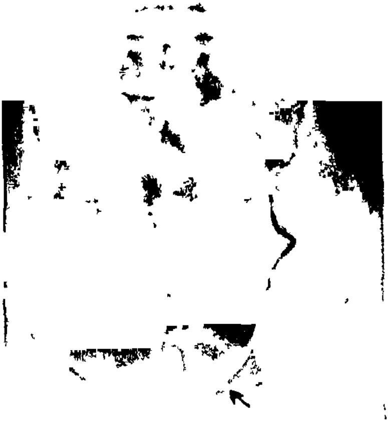

FIG 3

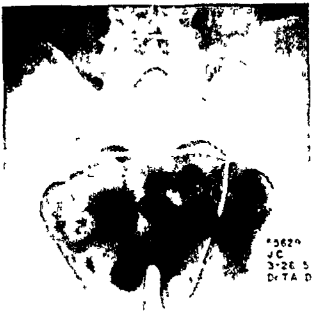

FIG. 4

FIG. 3. Loop formed in ureter

FIG. 4. Extractor has been passed up ureter, loop formed, withdrawn, and calculus engaged. Calculus then removed

Case of J. C. Calculus in lower end of left ureter. Under spinal anesthesia, March 26, 1953, a calculus extractor catheter was passed cystoscopically up the left ureter to the 20 cm. mark. The loop was formed, the catheter withdrawn, the calculus was engaged (fig. 4), and then removed to the bladder. It was removed from the bladder with a McCarthy panendoscope and forceps. The calculus measured 1.2 by .8 by .5 cm.

SUMMARY

A new instrument for the extraction of calculi from or dilatation of the ureter is described.

ADDENDUM

Since the presentation of this paper, stones have been removed from the lower ureter in fourteen consecutive cases, on the first trial, using the stone extractor herewith described.

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URETERAL REGENERATION: EXPERIMENTAL AND CLINICAL

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That the physiology and dynamics of ureteral regeneration is not clearly understood is evidenced by the many types of plastic repair attempted and by the high incidence of failure. The constriction of the ureter from aberrant vessels or hypertrophied musculature, or the very short stricture offers no problem in ureteral regeneration to the surgeon, but our studies are applicable to the longer strictures and to injuries involving the destruction of any considerable portion of the ureter. However, this group is large and we have found that many of the apparently short strictures involve a portion of the ureter at least 1 cm. long. It was the variation in the type of repair of such obstructions by the surgeon and their difference of opinion as to the proper time to continue the internal splint, from five days to five or six weeks, that led us to take the question to the experimental laboratory.

MATERIAL AND METHOD

Sixteen dogs, selected only for their proper size, were operated upon. The anesthesia was pentothal sodium and the skin preparation was tincture of iodine and alcohol. The usual lumbar approach was made, incising the latissimus dorsi and the external and internal oblique muscles. The transversalis fascia and transversalis abdominis muscle were split. The kidney was exposed by incising Gerota's fascia posteriorly. The peritoneum in the dog is tightly adherent to the anterior surface of the kidney and is thin and tears easily. If torn, the defect was sutured immediately. The renal pelvis of the dog is intrarenal, so a point was selected in the ureter from 0.5 cm. to 1 cm. below the kidney, and for a distance of 2 to 3 cm. distal to this point the ureter was completely excised except for a thin strip 2 to 3 mm. in width, but containing all the components of the ureteral wall. This presumably represents an extreme case of ureteral stricture or injury. An 8F red rubber catheter was passed through the middle calyx as a nephrostomy tube and well down into the distal ureter beyond the excised area to act as a splint. Small openings were made in this catheter to allow free drainage of the urine downward, but it was necessary to bury the proximal end under the fascia of the external oblique, for otherwise the dog would tear the tube out within a few days.

The 16 dogs were divided into groups of from two to five animals. In each group a nephro-ureterectomy was done after a lapse of two, three, four, and six weeks following the initial excision of the ureteral segment. The specimens included the kidney and the ureter to well below the injured segment. Sections were made for histological study at four levels; one definitely proximal to the excised segment; two actually through the area of excision; and one definitely below. Thus a comparison was obtained between the normal and the replaced

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Read at annual meeting, Western Section of American Urological Association, San Francisco, April 27–30, 1953.

area. Paraffin sections were made and stained with hemotoxylin and eosin. Four more dogs were operated upon later in the same manner, especially to check on the condition after four and six week intervals where we believed the maximum regeneration was likely to occur. The sections were made as previously, except that in four animals the section of the ureter were made longitudinally to include the normal ureter both above and below the excised segment. Marking sutures of black silk were placed at the extremities incorporating the splint to keep it from slipping and identify the injured area.

The purpose of the experiment was to observe 1) if a ureteral defect is replaced *over a ureteral splint,* 2) *what time is necessary for such replacement, and* 3) what type or types of tissue constitute this regenerated ureteral wall.

RESULTS OF OBSERVATIONS

In this study we were not interested in renal function and did not consider it; our operative technique was designed for the best splinting of the ureter and the observation of any ureteral replacement. We plan subsequent studies of the response of the kidney above the excised area.

The first group of dogs were those re-operated upon after two weeks. In one of these the excised area was marked with the cotton suture, and one dog had a pyelotomy. The hemotoxylin and eosin stains showed normal ureteral components, both proximally and distally, changing quite abruptly in the excised area (fig. 1). Here there was mucosa, although it was thinner than normal and markedly infiltrated with fibrin and inflammatory cells. No evidence of muscularis was present except in a very small segment of the cross section which was undoubtedly the narrow strip of ureteral wall left at the original excision.

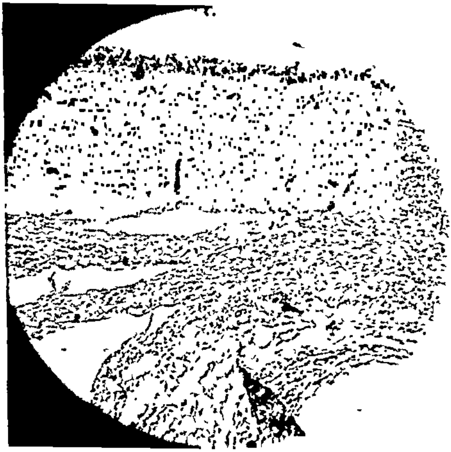

FIG. 1. Ureteral regeneration after 2 weeks

The wall showed marked edema with fibrin and necrotic material, polymorphonuclear leukocytes and lymphocytes.

The second group were re-operated upon at three weeks. Sections were observed in the same manner. Here the mucosa was reformed in the same manner as in the first group of animals, but strands of muscularis could be seen invading

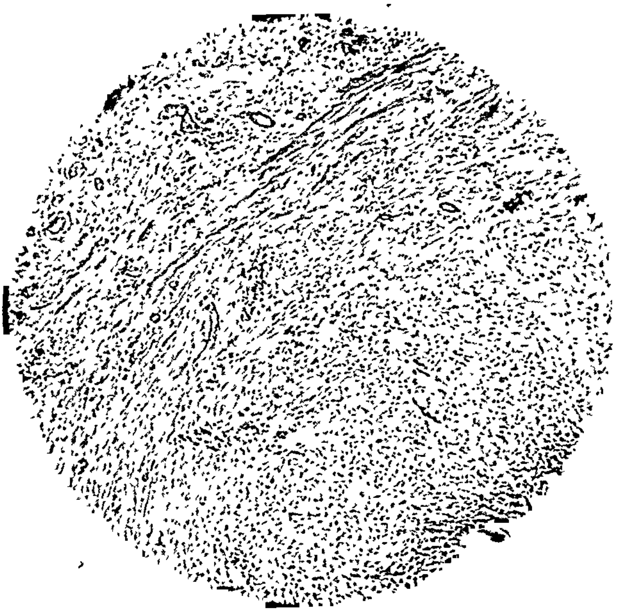

FIG. 2. Three weeks. Muscle strands appearing in regenerating area

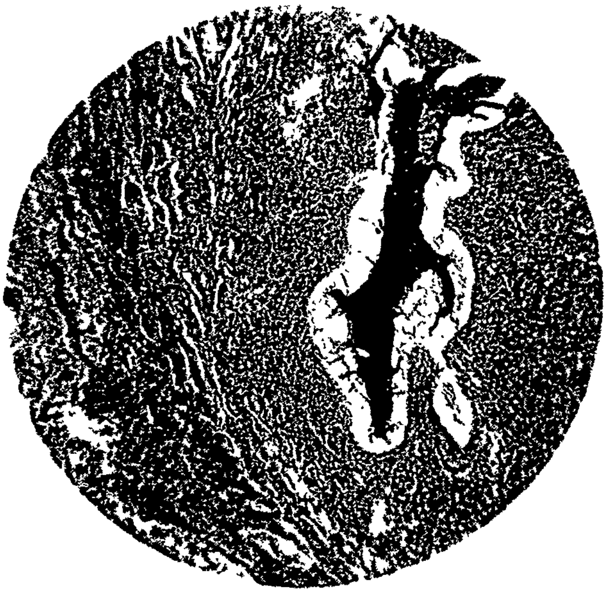

FIG. 3. Muscle strands appearing in inflammatory area after 3 weeks

the inflammatory area (fig. 2), and can be traced around the circumference of the ureter. In one of the specimens there was a patchy area of muscle tissue without confluence around the circumference. The confluent penetration of the muscle was most marked in those with least inflammatory reaction.

Four more dogs were operated upon after an interval of 4 weeks from the original procedure. No great difference was observed between this group and the dogs operated upon after three weeks. The same evidence can be seen of muscle strands invading the area of edema and inflammation (fig 3). The longitudinal section (fig 4) shows the strands of muscle again invading the excised area. Therefore our observation was that though a thin intact mucous membrane replacement is seen after two weeks, little or no evidence of muscularis can be identified at that stage However, muscle tissue is definitely present in varying amounts by the third and fourth weeks.

Since there was little change between the third and fourth week specimens, operation on the next group was deferred until six weeks after the original procedure. Here all components of the ureteral wall are present (fig. 5), although the muscularis shows a configuration different from the normal. The muscle tissue is thinner and does not have the mature thick block-like appearance seen in the normal ureter both above and below the excised area. We cannot yet say whether this is due to its immaturity or to the excessive inflammatory reaction. However, at six weeks all specimens showed permanent canalization of the ureter with mucosa and all muscular components of the wall present. In three of this group we had placed the No. 60 black cotton sutures at the proximal and distal ends of the excised area to identify accurately, both grossly and microscopically, the reformed tissue bridging the surgically made gap in the ureter. All these

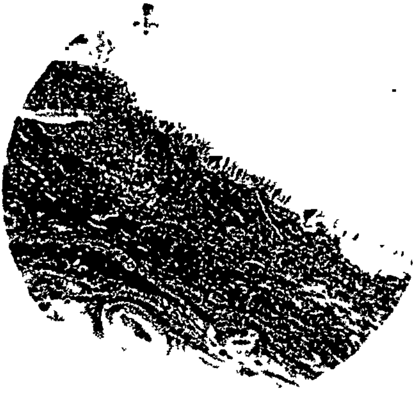

FIG 4 Longitudinal section of ureteral repair after 4 weeks

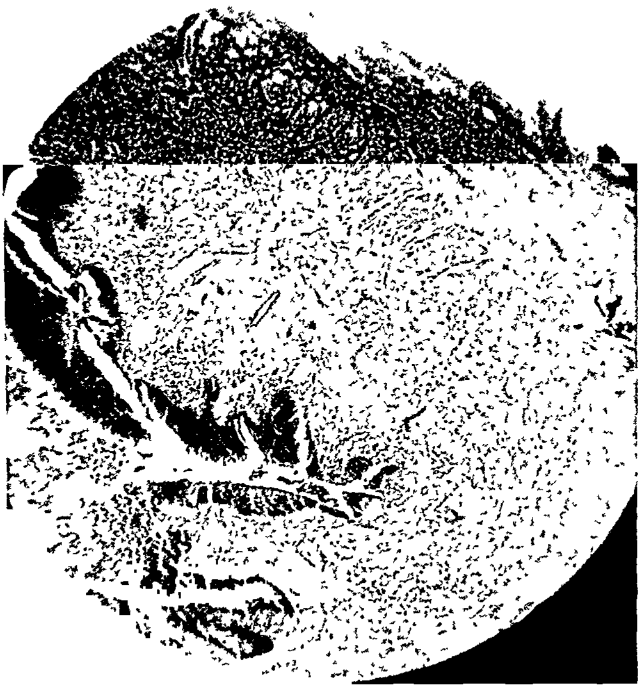

FIG. 5. Almost complete replacement of ureteral wall components after 6 weeks

sutures in the ureteral wall and through the rubber splint were found where they were originally placed six weeks before.

DISCUSSION

The most striking observation in this series was the rapid appearance of smooth muscle in the replaced tissue (three to four weeks), contrary to most of our concepts that smooth muscle does not regenerate to any extent. The whole experiment was plagued by extensive inflammatory and scar tissue reaction, doubtless due to the leakage of urine, since it was technically impossible with these dogs to allow any urine drainage except down the ureteral splint. The kidney, in most cases, appeared to be normal, and the microscopic sections confirmed this opinion.

We had some trouble in deciding whether this is an actual regeneration of ureteral components or only a sliding together of the cut ends. We did observe that the cotton sutures remained as far apart as when they were originally placed. Microscopically, at the 2 weeks' interval the mucosa has already bridged the gap, but there is no muscularis. This is particularly evident in the longitudinal sections. Likewise in the four week sections the muscularis can be seen in the longitudinal sections to be invading an area composed only of inflammatory tissue. Also we noticed that in the six week specimens the muscularis in the previously excised segment is markedly different in appearance than that of the areas both above and below. Moreover the cross sections and the longitudinal sections of the wall in those cases where the ends of the excised areas were approximated show an entirely different picture at the same time interval than those in which the ureteral gap was left open. This may be an academic point, for whatever the mechanism may be, we do see a continuous ureteral wall and a ureter capable of performing normally after an extensive and severe injury. This confirms the findings of David M. Davis in his work on intubated ureterostomy.

In dealing clinically with an injured or diseased ureter one is anxious to answer promptly the following questions:

1) Should the ureter be splinted?
2) Will the ureter reform to function again?
3) How long should the ureteral splint be left in place?
4) How large a defect can be repaired?
5) Will there be a resultant stricture, and can we expect a kidney above it to have sufficient function to support life alone?

These questions have been answered quite satisfactorily as follows:

1) The ureter must of course be splinted.
2) The data suggest that the time required is a minimum of six weeks, after which the splint may be safely withdrawn.
3) The ureter will reform with all its component structures and we know that clinically it will function adequately.
4) From our work we do not know just how large the defect may be that will be closed, but considering the proportionate size of the 50 pound dog and a man we feel that it can be quite extensive.
5) Clinically we have found no resultant strictures. We have felt so confident of our laboratory findings that since 1946, when the project was first begun, we have been splitting long strictures of the ureter over a catheter splint. Several cases are presented here for illustration.

CASE ABSTRACTS

Case 1. A man aged 27 who had moderate hydronephrosis associated with pain had a ureteral stricture 1.5 cm. in length beginning at ureteropelvic junction. The redundant pelvis was excised and the strictured area split throughout its length. A T-tube splint was used and was removed the sixth postoperative week.

Case 2. A 24 year old woman had advanced hydronephrosis associated with persistent pyuria. A stricture 2 cm. long was found at the ureteropelvic junction. The same procedure was followed and the splint removed after six weeks. Ten months later the urine was clear.

Case 3. A boy 4 years of age had bilateral advanced hydronephrosis. The left kidney was nonfunctioning. A 6 cm. stricture of the upper right ureter required almost completely denuding the ureter for 5 cm. T-tube was removed at the seventh postoperative week.

CLINICAL OBSERVATIONS

These patients all had long (1 to 7 cm.) strictures of the uppermost portion of the ureter. Definite diagnosis was made by opening the ureter and finding an inadequate caliber at the narrowed area. However, below the point of stricture the ureter readily admitted the splinting T-tube.

All plastic repair was done with minimal trauma to the cut edges, using plastic forceps and hooks. 00000 chromic catgut on atraumatic needle was used as suture material, as non-absorbable sutures are not suitable in this location. Four surgical principles have been followed meticulously: 1) Obtain dependent drainage of the ureteropelvic junction. 2) Remove all redundant renal pelvis to avoid stasis. 3) Splint the ureter for a sufficient period of time. 4) Keep the wound and the anastomosis dry and free from leakage of urine.

Our results have been uniformly satisfactory with preservation of the function of the kidney. Pyelography does not give an adequate picture of the situation, for a markedly distorted kidney with a large hydronephrosis before surgery does not quite return to our idea of a normal kidney after removing the obstruction. Our criteria of a successful procedure are 1) the patient must be symptom free, 2) the urine must be microscopically clear, 3) the pelvis must empty completely within 15 to 20 minutes after retrograde pyelography, 4) the kidney must have sufficient remaining function to support life, or at least 25 per cent of the total function, and 5) one should be able to pass a 10F or 12F bulb ureteral catheter to the kidney pelvis without obstruction.

The postoperative management of the T-tube consists of attaching its end to a rubber glove, allowing the kidney to drain either through the nephrostomy or the ureter. We have had little febrile reaction and no blocking of the catheter. We have used nephrostomy drainage rather than pyelostomy, as recommended by Davis, as very little renal parenchyma is damaged and we believe that the drainage is better. In a series of 20 cases treated in this way no irrigations have been done and no calcium deposits have occurred to trouble us. The nephrostomy wound closes spontaneously within 24 hours without urinary drainage and the urine should be free of pus by the end of the fourth week after the T-tube is removed.

SUMMARY

Experimentally the ureter shows a marked ability to regenerate all its components.

The mucosa is rapidly replaced, with the muscularis filling in more slowly up until six weeks, when nearly normal components are present.

Clinically we have utilized our experimental knowledge in splinting large defects without reservation, confident of the adequate function of the kidney and ureter involved.

Investigation of the type of peristalsis and of the amount of periureteral fibrosis will be done in future experiments.

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PLASTIC REPAIR OF URETEROSIGMOIDOSTOMIES

HOMER W. HUMISTON

A 45 year old man was initially seen in March 1950, for gross hematuria which had occurred 1 year and 1 week previously. Cystoscopic inspection revealed several square centimeters of the bladder involved with low grade papillary carcinoma. Attempts to deal with the growth transurethrally failed. A transvesical fulguration was done, which was supplemented with additional transurethral fulguration. Six months of these efforts had failed to control the tumor. On September 6, 1950, bilateral ureterosigmoidostomies and a total cystectomy were performed in one stage. The transplants were done by the Coffey 1 technic. Preoperatively, the patient had had no symptoms except hematuria, his blood chemistry was normal, and excretory urography revealed a normal upper tract bilaterally.

For the next 11 months he felt under par, although he worked fairly consistently as a salesman. He would have a degree or more of fever approximately two days out of three. He had several episodes of chills and high fever for which he was hospitalized, a rectal tube placed, and intensive antibiotic therapy prescribed. He consistently described an increasing thirst which he could not satisfy, and failure to regain his strength and endurance. Two months after cystectomy his blood urea nitrogen was 28.9 mg. per cent; 2 months later it was 22.0 mg. per cent; and 4 months later it was 33.6 mg. per cent.

On August 17, 1951, eleven months after cystectomy, the low midline incision was reopened after bowel preparation with aureomycin. No recurrence of the bladder tumor could be demonstrated. A colotomy was done on each side, and the transplants were explored and dealt with through the lumen of the bowel. On the left, no stoma could be found. The dilated ureter was visualized through the bowel mucosa, and was incised for 1 cm. longitudinally. Interrupted sutures of 5-0 chromic were used to bring mucosa to mucosa. There remained a stoma estimated to be 30F. This colotomy was then closed. On the right it was found that the intraluminal stump of the ureter had failed to slough, and was a fibrotic strictured stub about one centimeter long. The ureter above this stub was dilated. The stub was amputated and the ureter was incised about 1 cm. longitudinally, as had been done on the left, and mucosa-to-mucosa sutures were placed. The colotomy was then closed. The postoperative course was entirely uneventful. After a few days the blood urea nitrogen was 12.0 mg. per cent. Since this operation 20 months ago, the patient has felt as well as he did a few years ago, has no abnormal thirst, and has regained his strength and endurance. On April 14, 1953, his blood urea nitrogen was 26.4 mg. per cent, creatinine 1.5 mg. per cent, CO_2 combining power was 36 volumes per cent, and the blood chlorides 714 mg. per cent.

The line drawings traced from the excretory urograms are shown in figures 1 and 2. The hydronephrosis following the anastomoses was more severe on the

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Read at annual meeting, Western Section of American Urological Association, San Francisco, April 27–30, 1953.

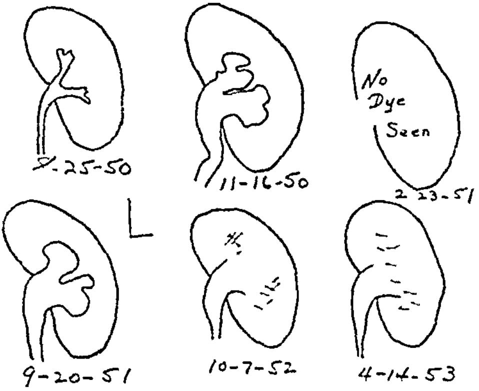

Fig 1

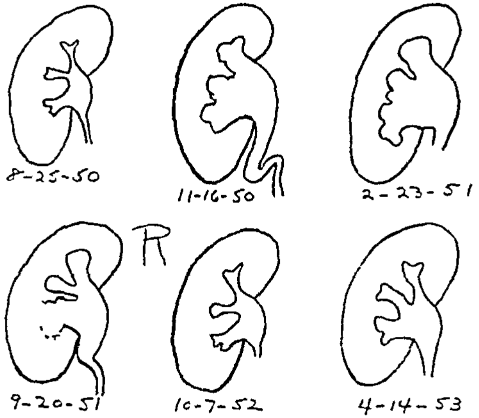

Fig 2

left, and the improvement following the plastic repair was substantially better on the right

DISCUSSION

Stricture of the terminal ureter occurs not infrequently following ureterosigmoidostomies regardless of the technique used in making the anastomosis It is believed that the incidence of stricture is less when the bowel mucosa is sutured directly to the terminal ureter, but this complication is not thereby eliminated The plastic procedure which was used in this instance is applicable only if the ureterosigmoidostomy has been performed by one of the tunneling techniques

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ELECTROMYOGRAPHY OF THE URINARY BLADDER

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The recording of bio-electric potentials from the musculature of the urinary bladder was initially attempted because of the recognized shortcomings of the conventional cystometrogram.[1, 2, 3] It was also hoped that such electromyographic evaluation might indicate the functional state of the viscus with a degree of sensitivity not heretofore attained.

To this end, transurethral electrodes were so designed (fig. 1) that they might be brought in contact with the lateral walls of the bladder and changes in electro-potentials recorded on a Grass electro-encephalograph suitably filtered. In a series of studies on human subjects[4, 5, 6] it was found that electromyograms so obtained possessed definite and typical characteristics and further that striking and recurring abnormalities in the records were observed in known pathological states.[7] It was, moreover, determined that intravesical pressure changes paralleled the bio-electric shifts. Therefore, electromyography appeared to represent a highly sensitive method for ascertaining the physiological condition of the bladder in diseased states.

Although strong evidence indicated that the records obtained represented true bio-electric potentials arising within the vesical musculature, this evidence was of an indirect nature,[5] and it was therefore deemed desirable to perform experiments of a conclusive character in order to determine whether the electromyograms as obtained *in situ* from the human subject did, in fact, represent potential shifts without artefacts arising solely from the bladder musculature and not from other tissues. It was also thought that laboratory studies might clarify, to a large extent, our fundamental knowledge concerning the origin of the characteristic bio-electric potentials observed.

To this end isolated bladders from a variety of mammalian forms (dogs, cats, rabbits, guinea pigs and rats) were utilized.[8] The animals being sacrificed by means of a blow on the head to eliminate the known effects of anesthesia. These bladders were quickly dissected, including short portions of the ureters and urethra, and were suspended (with fine silver electrodes attached) in a bath of oxygenated Sollmann's solution at 38 degrees centigrade. The electromyograms obtained from such preparations were found, in all respects, to be indistinguishable in contour from those recorded *in situ* from the human subject (fig. 2, *A* and *B*).

Read at annual meeting, American Association of Genito-Urinary Surgeons, Hot Springs, Va., May 6-8, 1953.

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myograms are representative of either a) faulty parasympathetic innervation, or b) an atypical response of the diseased musculature to parasympathetic bombardment.

SUMMARY

Electromyograms obtained from the isolated urinary bladders of various mammalian types are indistinguishable in form from records secured *in situ* from normal human subjects.

The frequency of activity as well as the magnitude of bio-electric potentials observed in excised bladder preparations were increased by the administration of parasympathomimetic drugs and by adrenergic blockade. The reverse was found to be true for sympathomimetic substances and parasympathetic blockade.

Records secured from strips of human bladder musculature (fig. 2, *C*) were identical in contour to those obtained from isolated whole bladders, or from the human bladder *in situ*. Maximum activity was shown by tissue samples from the more central portions of the bladder and electropotential activity was minimal in tissue strips from the dome and from the vesical neck.

These findings indicate that the electrocystomyogram secured by way of transurethral electrodes placed within the human bladder represents vesical activity in response to parasympathetic bombardment.

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INTESTINOVESICAL FISTULA: REPORT OF SIX CASES

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Intestinovesical fistula has interested physicians for generations, a description of the condition having been reported in the second century. Harrison Cripps, in his classic monograph, accurately defined and classified this disease entity in 1888. The condition must no longer be considered infrequent as evidenced by the more than 700 case reports since that time. The diagnosis and treatment command the attention of urologists. It is the purpose of this paper to present 6 cases emphasizing the diverse aspects of the disease. We have chosen to use the term "intestinovesical fistula" as advocated by Barnes and Hill. From a semantic viewpoint this is correct as it not only denotes the usual direction of the pathological process, but is also applicable to all portions of the intestinal tract.

CLINICAL FEATURES

During recent years the sex distribution reveals an increasing preponderance of males affected. This is based upon two sound considerations: first, the virtual elimination of pelvic inflammatory disease in the female with the introduction of the modern chemotherapeutic and antibiotic drugs, and, secondly, the barrier to fistula formation offered by the interposition of the uterus and adnexae between the bowel and the urinary bladder. Age distribution favors the middle and older age groups because of their higher incidence of neoplasm and diverticulitis of the colon. It is evident from all studies that a rational classification is based on etiology, namely: 1) traumatic, 2) congenital, 3) neoplastic and 4) inflammatory. Surgery most often accounts for the traumatic fistulas encountered in civilian practice. Congenital fistulas are rare and almost invariably associated with congenital imperforate anus. Neoplastic fistulas result from a multitude of primary lesions arising in the genito-urinary and lower intestinal tracts. Inflammatory fistulas also result from numerous causes, but of paramount importance and interest is diverticulitis of the colon. Diverticulitis is truly a widespread disease. This is apparent from the finding that 5 to 8 per cent of patients with symptoms sufficient to warrant roentgenological examination, demonstrate evidence of diverticulosis. Approximately 20 per cent of those with diverticulosis have associated diverticulitis.

SYMPTOMS AND DIAGNOSIS

The pathognomonic symptoms of intestinovesical fistula are referable to the urinary tract. Pneumaturia and the passage of feces per urethram, when associated with dysuria, urgency, frequency, hematuria and suprapubic pain, leave little doubt as to the diagnosis. The remainder of the clinical picture will be determined by the exact nature of the underlying etiology. Urinalysis will generally

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Read at annual meeting, Western Section of American Urological Association, San Francisco, April 27–30, 1953.

reveal various degrees of pyuria, bacilluria, hematuria and fecaluria. Cystoscopy has been shown to be the most informative diagnostic procedure. However, actual visualization of the fistulous opening is not always possible. Often one merely gains presumptive evidence in the form of a localized area of cystitis and edema. The cystogram may provide an exact diagnosis by revealing an extravesical extension of the contrast medium into the bowel. Barium enema aids in the diagnosis of the underlying bowel disease but is much less efficacious in depicting the actual fistula. Sigmoidoscopy is even less informative in this regard. The use of various dyes to demonstrate a communication between the intestinal tract and the bladder has been of value in some cases. In spite of all these diagnostic adjuncts, however, the actual demonstration of the fistula many times must await surgical exploration. It should be emphasized that, given the pathognomonic symptoms, a diagnosis of intestinovesical fistula must be maintained even though objective substantiation is lacking.

Recognition of an "incipient fistula" is equally important. The appearance of dysuria, urgency, frequency and tenesmus in a patient with intestinal disease precedes the development of the fistula in many cases. Adequate treatment during this phase of the disease may prevent the subsequent fistula formation.

CASE REPORTS

Case 1. J. O., No. 22652, a 59 year old white man, was admitted to the Long Beach Veterans Administration Hospital on October 29, 1951, in a semi-comatose condition with symptoms of an intractable cystitis of 2 months' duration. A past

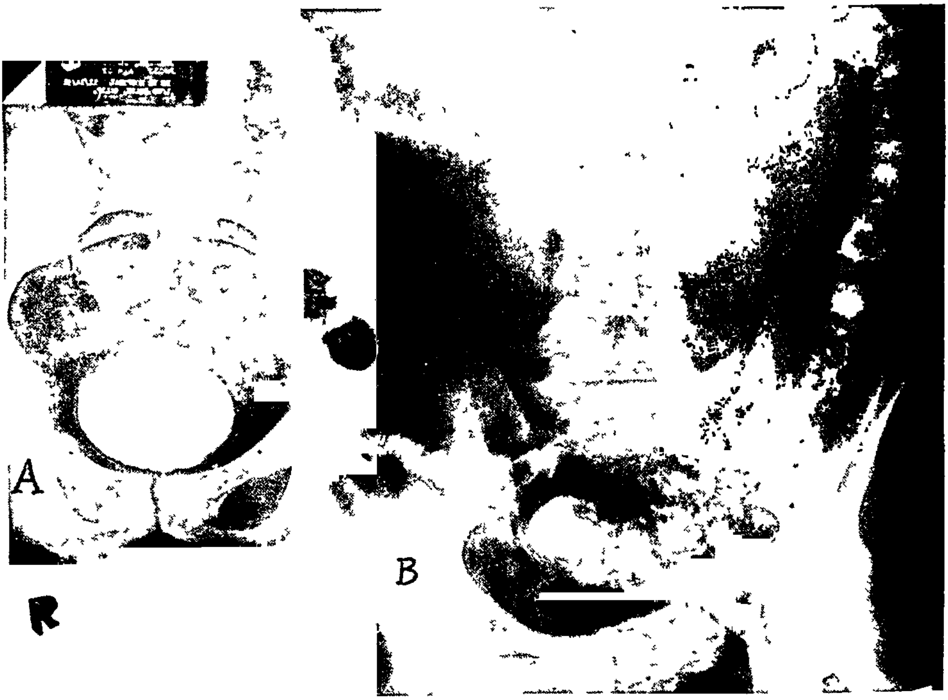

FIG. 1. *A*, cystogram fails to reveal fistula. *B*, barium enema discloses diverticulosis of colon.

history of "nephritis" and pulmonary tuberculosis was elicited. Physical examination revealed a chronically ill, dehydrated patient with moderate tenderness in the left costovertebral angle. The prostate was slightly enlarged, very soft and tender.

Initial laboratory studies revealed blood urea nitrogen of 127 mg. per cent and a CO_2 combining power of 7 meq/L. Urinalysis revealed numerous leukocytes, 10-12 red blood cells and many coarse granular casts. Urine culture revealed a moderate growth of A. aerogenes.

Cystoscopy on November 4, 1951, revealed an area of cystitis and edema surrounding the left ureteral orifice. A small amount of fecal material was present but a definite fistulous opening could not be identified. Cystogram disclosed an irregular outline suggesting cellule formation but no fistula was demonstrated (fig. 1, *A*). Proctoscopy following intravesical instillation of methylene blue failed to demonstrate the fistula. Barium enema disclosed diverticulosis of the colon (fig. 1, *B*). An organic carmine dye, which is not absorbed from the intestine, appeared in the urine four hours after oral ingestion. Careful anamnesis at this time brought out a definite history of pneumaturia and passage of feces per urethram.

On January 2, 1952, surgery revealed extensive diverticulosis of the colon with an area of diverticulitis extending downward from a point 6 cm. above the peritoneal reflection. The involved segment measured 10 cm. in length and a definite fistulous tract was found to communicate with the left posterior vertex of the bladder. The fistula was divided, the bladder closed and an anterior resection without diversional colostomy was performed.

The postoperative course consisted of chronic pyelonephritis with increasing renal insufficiency, chronic acidosis and nephrolithiasis. At no time was there any further difficulty from the sigmoidal-vesical fistula. Cystoscopy and cystogram 14 months later revealed no evidence of fistula.

Case 2. H. S. M., No. 14419, a 43 year old white man with post-traumatic hemiplegia and aphasia, experienced sudden severe lower abdominal pain during defecation. Urinary tenesmus was followed by acute retention. Catheterization

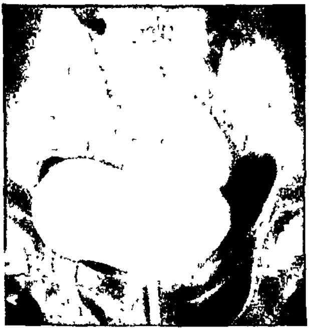

FIG. 2. Cystogram discloses contrast medium extending from bladder into colon

revealed grossly bloody urine. On October 24, 1950, the fifth day of illness, the patient was transferred to the Long Beach Veterans Administration Hospital.

Physical examination revealed an extremely dehydrated, acutely ill patient. The abdomen was distended and tympanitic. Diffuse tenderness with spasm and rebound tenderness in the LLQ was present. Bowel sounds were absent.

Cystogram disclosed a definite vesicocolic fistula (fig. 2). Cystoscopy revealed a 5 mm. opening, with necrotic grayish-white margins, in the left posterior aspect of the vertex. On October 25, 1950, a transverse colostomy was done and a generalized peritonitis due to E. coli was found.

Six months later the cystogram of the asymptomatic patient revealed a smooth contour and no evidence of the previously demonstrated fistula. Barium enema and sigmoidoscopy were normal. On May 23, 1951, laparotomy revealed only old inflammatory adhesions between the recto-sigmoid and bladder and the colostomy was closed.

Case 3. K A. S., No. 33157, a 35 year old white man, was admitted to the Long Beach Veterans Administration Hospital on July 9, 1952, complaining of urinary frequency, urgency, dysuria, terminal pneumaturia and passage of food particles per urethram. A subtotal colectomy with permanent ileostomy had been performed 9 months previously following unsuccessful medical management of chronic ulcerative colitis (fig. 3, *B*).

The patient was poorly nourished and chronically ill. He had a healed surgical scar with an ileostomy in the right lower quadrant. A small amount of purulent drainage was present at the site of the previous colostomy.

Repeated urinalyses revealed 1 plus albumin, numerous leukocytes, 10–15 red

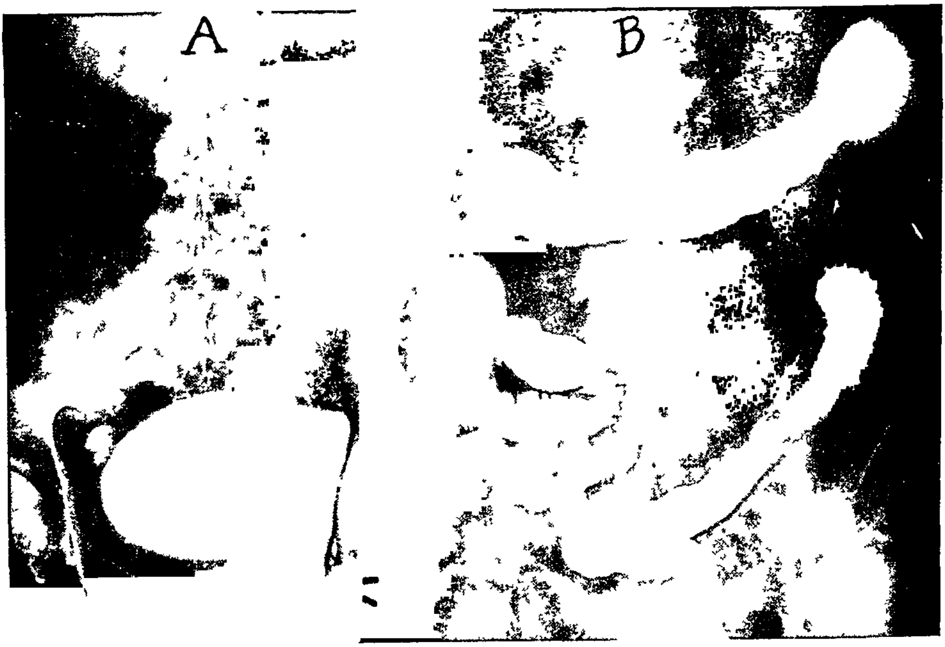

FIG. 3 *A*, cystogram fails to disclose fistula. *B*, barium enema discloses typical appearance of chronic ulcerative colitis

blood cells and numerous motile bacteria. Cystogram, including films delayed by 30 and 60 minutes, failed to demonstrate extravesical extension of contrast medium (fig 3, *A*). Cystoscopy showed a small, circumscribed area of bullous edema 4 cm. posterior and lateral to the right ureteral orifice. A toothpaste-like material was seen to extrude from the lower margin of this area. Below this point a small diverticulum of the bladder wall was noted.

Surgery on July 28, 1952 disclosed dense inflammation about the distal loops of ileum with a well organized abscess cavity adherent to the bladder. A fistulous tract led into the abscess cavity and originated 10 cm. proximal to the ileostomy. Two additional small ileo-ileal fistulae were identified. The terminal 30 cm. of ileum were resected and the opening in the bladder was closed. The patient was free from urinary symptoms nine months later.

Case 4. C. P., No. 35211, a 51 year old white man, entered the Long Beach Veterans Administration Hospital with severe pain in the left lower quadrant and tenderness radiating to the suprapubic region. Similar episodes had occurred 5 times in the past 6 years. Ten months prior to admission, pneumaturia and dysuria developed

Physical examination revealed an acutely ill patient with marked tenderness in the left lower quadrant and suprapubic region. Barium enema revealed diverticulitis of the colon (fig 4, *B*).

On August 22, 1950, a transverse colostomy was performed, followed by daily irrigations of the distal loop with sulfathaladine solution. Two weeks later cystoscopy and cystogram (fig. 4, *A*) failed to reveal evidence of intestinovesical fistula, but bilateral vesico-ureteral reflux was noted. Methylene blue instilled into the bladder was recovered from the distal loop. The patient failed to return for definitive surgery until 27 months later. During this interval he had been working and was free of symptoms except for two episodes of cystitis

Surgery on October 7, 1952, demonstrated diverticulosis with a definite di-

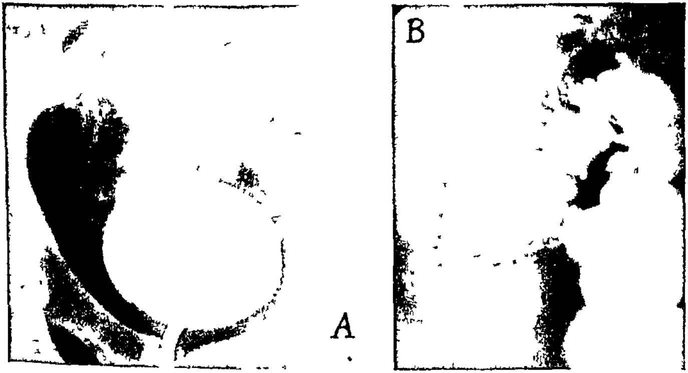

Fig 4 *A*, cystogram fails to disclose fistula, but bilateral vesico-ureteral reflux is apparent *B*, barium enema demonstrates diverticulitis

verticulitis involving the sigmoid 6 cm. above the peritoneal reflection. The sigmoidal-vesical fistula was divided and an anterior resection performed. The colostomy was closed 22 days later. Although peritonitis and wound evisceration complicated the postoperative period, the patient was ultimately discharged without further urinary symptoms.

Case 5. H. P. W., No. 38646, a 71 year old white man, was admitted to the Long Beach Veterans Administration Hospital on December 13, 1951, complaining of rectal bleeding, abdominal pain and a change in bowel habits. Rectal examination showed induration at the base of the bladder on the left but no mass was palpable.

On urinalysis 10–15 leukocytes and a rare red blood cell were found. Stools were positive for occult blood. Repeated barium enemas were unsatisfactory because of complete obstruction at the rectosigmoidal junction (fig. 5, *B*). Urologic consultation elicited a history of increasing cystitis with pneumaturia and passage of feces per urethram. Cystocopy revealed an intense diffuse cystitis with marked spasm and reduction of capacity. A 2 cm. opening on the left lateral wall of the bladder was seen and proved to be an intestinovesical fistula on cystogram (fig. 5, *A*).

On June 11, 1952, a preliminary transverse colostomy was performed following which the urinary symptoms subsided. Definitive surgery on August 11, 1952 disclosed a large ulcerated carcinoma of the sigmoid, 10 cm. above the peritoneal reflection, which invaded the bladder. An anterior resection of the lesion was done, the opening in the bladder closed, and a suprapubic cystostomy performed.

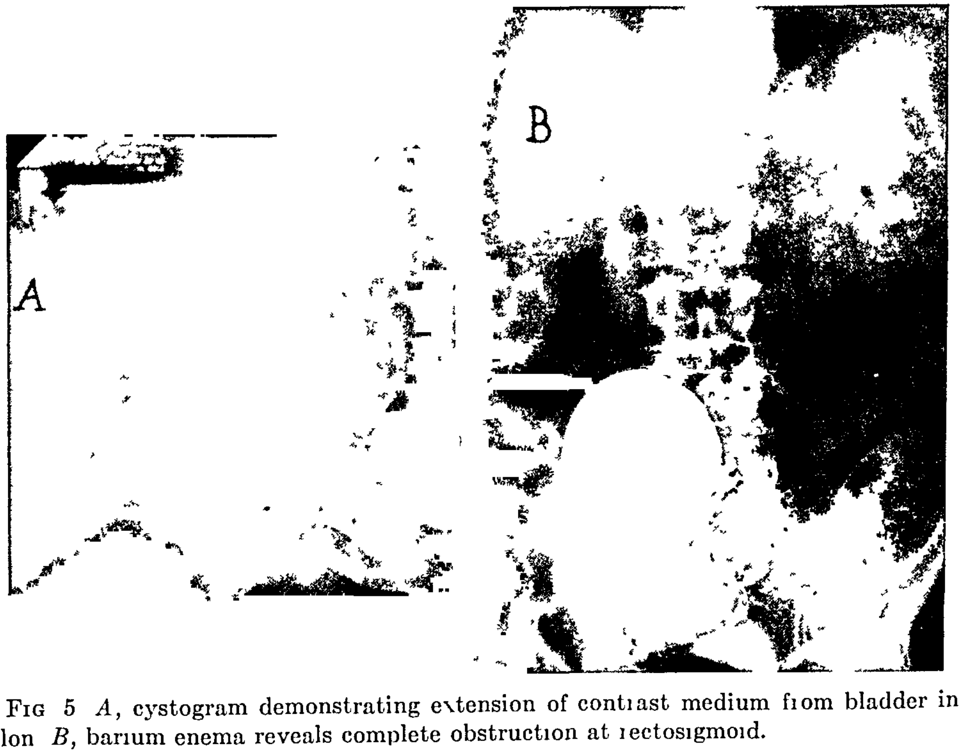

FIG 5 *A*, cystogram demonstrating extension of contrast medium from bladder into colon *B*, barium enema reveals complete obstruction at rectosigmoid.

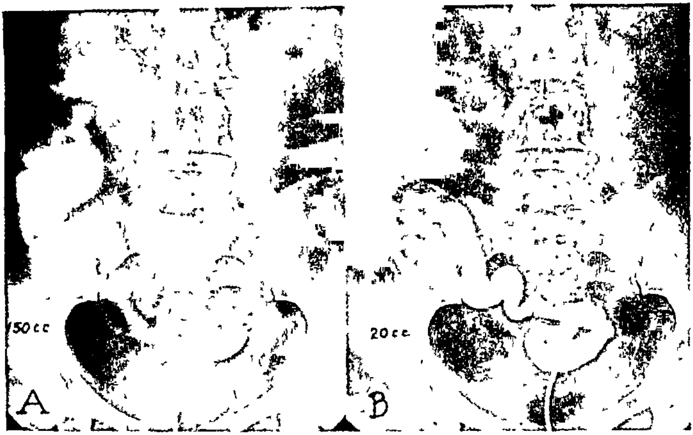

FIG. 6. Injection of contrast medium into fistulous opening in bladder outlines ileum and reflux into colon with increased volume of medium (Courtesy of Dr. S K Bacon.)

Two months after discharge the patient returned with a recurrent suprapubic urinary fistula. The urine was heavily infected. Cystostomy drainage was reestablished. On February 9, 1953, acute pulmonary edema developed and failed to respond to cardiac treatment; death occurred 2 days later. Necropsy revealed residual carcinoma in the colon, a huge cauliflower mass of tumor extending into the bladder and distant metastases in the liver.

Case 6. F. W. M., No. 42386, a 40 year old white woman, entered the Long Beach Veterans Administration Hospital with a history of pneumaturia and passage of feces per urethram following peritoneoscopy for lysis of adhesions A history of nine previous surgical procedures was elicited.

A fistulous opening was seen on cystoscopy prior to admission. Catheterization of this opening with injection of contrast media clearly defined an ileovesical fistula (fig. 6). Neither small bowel studies nor barium enema demonstrated this fistula.

On March 25, 1953 the ileovesical fistula was divided, the bladder closed and the involved segment of terminal ileum resected.

DISCUSSION

Our experience with 6 cases of intestinovesical fistula is in accord with previous studies. Pneumaturia and fecaluria were diagnostic and present in all cases except case 2 which was of an emergency nature with an unreliable history. This patient is similar to one reported by Harlin and Hamm in whom inability to void was the primary urologic symptom associated with an acute perforated diverticulitis.

Cystoscopy was the most reliable diagnostic procedure. The fistulous opening was actually visualized in 4 cases. The clue to diagnosis was the finding of feces

TABLE 1.—*Relative merit of various findings in establishing a diagnosis of intestinovesical fistula*

CASE	CYSTOSCOPY	BARIUM ENEMA	CYSTOGRAM	DYES	PROCTOSCOPY	PNEUMATURIA	DIAGNOSIS & TREATMENT
J. O. No. 22652	Positive (Feces in bladder plus localized area of cystitis)	Negative	Negative	Positive	Negative	Positive	Diverticulitis One stage resection Cure
H. S. M. No. 14419	Positive (Fistula visualized)	Not done	Positive	Not done	Not done	?	Acute perforation diverticula Colostomy alone Cure
K. A. S. No. 33157	Positive (Fistula visualized)	Not done	Negative	Not done	Not done	Positive	Ulcerative colitis Resection & ileostomy Cure
C. P. No. 35214	Negative (Not done until two weeks after colostomy)	Negative	Negative	Positive	Not done	Positive	Diverticulitis 3 Stage resection Good 3 mos. post-op.
H. P. W. No. 38646	Positive (Fistula visualized)	Negative	Positive	Not done	Negative	Positive	Carcinoma 3 Stage resection Death
F. W. M. No. 42386	Positive (Fistula visualized)	Negative	Positive	Not done	Negative	Positive	Traumatic One stage resection

in the bladder in an additional case. The one instance of a negative cystoscopic finding concerns the case in which cystoscopy was delayed until 2 weeks after diversion of the fecal stream. While barium enema failed to demonstrate the fistula in any of the cases, it was very helpful for the diagnosis of the underlying bowel disease. The use of dyes was helpful in two cases. The contribution of proctoscopy and sigmoidoscopy proved to be of no value. These data are summarized in table 1.

Recognition of the underlying disease responsible for the intestinovesical fistula is the prime consideration in surgical management. In general, a multiple stage procedure with preliminary colostomy is the treatment of choice. In carefully selected cases with minimal inflammatory involvement, a one-stage resection without colostomy offers good results with less morbidity. A cure by colostomy alone was obtained in one case, and in all cases symptoms were relieved by colostomy. Our case with carcinoma of the colon confirms the experience of others, namely, that palliation is usually all that can be accomplished. The prognosis in carcinoma of the colon has been shown to be considerably poorer when involvement of the bladder is present. With an actual intestinovesical fistula lined by carcinoma cells, the prognosis is almost uniformly fatal.

SUMMARY

The clinical features of intestinovesical fistula are reviewed.

Six cases, illustrating various primary etiologic diseases, are presented.

The importance of pneumaturia and fecaluria is emphasized. Cystoscopy is the most informative diagnostic procedure.

Treatment, in most cases, consists of multiple stage surgery with preliminary colostomy. However, in selected cases, a one stage resection is advocated.

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UTEROVESICAL FISTULA WITH FETAL PARTS PRESENTING IN EXTERNAL URETHRAL MEATUS

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It was of interest to learn, in review of the literature, that before this same organization and in the same state of Virginia, MacKenzie in 1921 presented a paper on the same subject of uterovesical fistula. Presenting circumstances however were considerably different. As late as 1950 Stening stated, "this type of fistula is so rare that it does not find a place in most manuals of obstetrics and gynecology." We were not in complete agreement with this statement because several case reports were encountered. A rather diligent probe of all publications back to 1876 on the subject of uterovesical fistula fails to reveal a single instance where fetal parts were demonstrable within the bladder and presenting through the urethra as a complication of the pregnancy.

The girl's history was quite informative. A 30 year old white female gravida 4, para 0, presented herself to her family physician August 20, 1951 approximately 6½ months pregnant for prenatal care. Her past history revealed that her first pregnancy was 11 years prior to this time. Her labor was difficult and her child died as a result of toxemia of pregnancy. Her old hospital record said that she leaked urine from her vagina following delivery and returned in 3 months for vaginal repair of a vesicovaginal fistula. Apparently the uterovesical fistula was unrecognized. Since that time, 11 years ago, menses had stopped but cyclic voiding of blood in the urine occurred every month and has persisted to date. She did not need to wear a pad and it was not necessary to interrupt intercourse. Three years later a cesarean section was done for a 6 months dead fetus. She stated that 5 years later she miscarried a 3 months pregnancy through her bladder.

The examination at this time (August 20, 1951) by her family physician showed everything to be essentially within normal limits except that fetal heart tones could not be heard. Blood Kahn was negative. One week later she was admitted to the Methodist Hospital because of lower abdominal cramping interpreted to be uterine contractions. A vaginal examination demonstrated a long, thick cervix with no dilatation. No fetal heart tones could be heard. A torn fetal scalp could be seen coming from the urethra. At this stage we were called to see the patient for the first time (fig. 1). Cystoscopic examination revealed loose pieces of the scalp of the dead fetus with broken pieces of head bones. Visualization at this time was considerably impaired due to the space-occupying foreign body in the bladder. General surgical consultation advised open section which was done immediately. The uterus was closed, a tubal ligation performed but no attempt made to repair the fistula at this time. This was the judgment of the surgeon as he felt the patient's general condition precluded further surgery. Her postoperative course was uneventful and all lochia was discharged through the bladder. An excretory urogram prior to her dismissal on the seventh post-

Read at annual meeting, American Association of Genito-Urinary Surgeons, Hot Springs, Va. May 6–8, 1953.

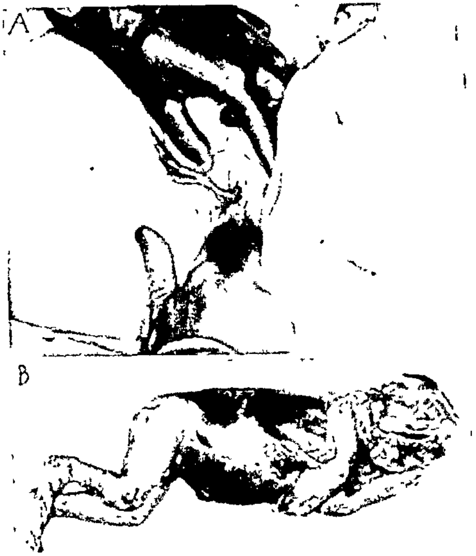

FIG. 1. *A*, fetal scalp emerging from urethra. *B*, dead fetus as it appeared following cesarean section. Note absence of scalp and broken head bones.

operative day showed a normal upper urinary tract. Arrangements were made for her to be re-admitted to the hospital in approximately 3 months' time for repair of her fistula.

Approximately a year later the patient entered the hospital again. Cystoscopic examination showed normal bladder with a fistula opening on the posterior wall in the midline. Repeated cystograms failed to demonstrate communication with the uterus. Upper tract studies were again normal. Urinalysis was negative. On October 1, 1952, through a midline incision, the bladder was opened, the fistulous tract excised and the uterus removed leaving the cervix. The bladder was closed and drained with a urethral catheter. The patient's postoperative course was again without complication and the urethral catheter was removed on the tenth day. She was discharged on the fourteenth day. Follow-up cystoscopy was done one month later and a normal bladder found. There was no urinary difficulty.

COMMENT

From the published data nearly all uterovesical fistulas were secondary to obstetrical procedures or sequelae of radium application, surgical accidents, carcinoma and occasionally tuberculosis. The uterine opening is rarely found in the corpus uteri but nearly all were located in the cervical canal which gave the patient vaginal leakage of urine. There was no vaginal leakage of urine present in our case, therefore placing the opening above the internal os. The conclusions reached by Sims in 1928 summarize well this subject. I see no reason today to vary his remarks which are as follows:

1) Uterovesical fistulas may be due to trauma in labor with the use of forceps, either by carelessness or incompetence especially in attempt at rotation.

2) They may be caused by uninterrupted prolonged labor with the head on the pubic rami and bladder with strong uterine contractions.

3) According to the histories of the reported cases the complication was not caused by the accoucheur, though he may be reluctant to report in the majority of instances.

4) Practically all fistulas occurred in cases of prolonged labor, contracted pelvis, or a combination of the two, with the bag of water rupturing several hours previous to delivery.

5) The use of pituitary extract may play a part.

6) The incidence is probably more frequent than is observed or reported.

CONCLUSIONS

A case has just been described of a 30 year old white woman 6½ months pregnant, presenting fetal parts in the urinary bladder and through the external urethral meatus.

Several instances of uterovesical fistula have been reported, as evidenced in the bibliography, but to our knowledge ours is the first with this added feature.

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THE TREATMENT OF PRIMARY CARCINOMA OF THE BLADDER

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We have consistently leaned toward conservative treatment of bladder cancer because the results reported from cystectomy and ureterosigmoidostomy have not been sufficiently impressive to convince us that equally good or better results may not be obtained from less radical methods. Recent contributions by Creevy,[1] Kligerman et al.,[2] Colby and Kerr[3] and others serve to sustain this opinion. Reports dealing with the late results of uretero-intestinal anastomosis have now appeared in sufficient numbers to emphasize the prevalence of subsequent renal failure even in the few cases in which the cancer has appeared to have been controlled. (A repetition of quotations designed for argument from either viewpoint of this important subject will serve no pertinent purpose.)

The degree of malignancy and the extent of growth in a tumor are primary factors upon which intelligent treatment will be based. The determination of these factors with a fair element of accuracy is difficult. In the case of bladder tumors, the location of the lesion within the organ must also be considered, along with the age and general condition of the patient. Fortunately in this day of advanced surgical techniques, antibiotics and ancillary services, primary surgical mortality is much less to be feared than was formerly the case. This may at times lead one to use radical methods without due regard for late morbidity or mortality. Conversely, cancer is a deadly disease and every reasonable effort should be made to entirely remove or destroy the tumor. Each case is to be considered an individual problem with the surgeon assuming the role of the good doctor in his efforts to do all that the case requires commensurate with safety and the ultimate welfare of the patient.

In considering the degree of malignancy of a given bladder tumor, the appearance at cystoscopy will usually differentiate those of the two extremes. The pedunculated papilloma with a long pedicle is practically always benign and while it may recur from transplantation it is not invasive and is not to be considered malignant. The sessile type and those papillomas with short broad bases must be regarded as likely malignant. A biopsy taken from the base of any of these growths and submitted to pathological study will permit a more accurate evaluation of the degree of malignancy as shown primarily by the tendency of the tumor cells to invade the bladder wall. The majority of cases will fall in the latter category.

This fact tends to stress the importance of the pathological report. Jewett,[4] Marshall[5] and others have emphasized the importance of the degree of penetration as related to treatment and prognosis. This must be kept in mind in securing

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Read at annual meeting, Southeastern Section of American Urological Association, Havana, Cuba, March 26–29, 1953.

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[2] Kligerman, M. M., Robinson, J. N., Fish, G. W. and David, I.: J. Urol., **68:** 706, 1952.

[3] Colby, F. H. and Kerr, W. S.: N. Eng. J. Med., **244:** 504–506, 1951.

[4] Jewett, H. J.: J. Urol., **67:** 672, 1952.

[5] Marshall, V. F.: J. Urol., **68:** 714, 1952.

the biopsy specimen. The resectoscope loop employing a very high frequency current is our best available instrument for this purpose. However, it is far from ideal. In dealing with the flat invasive tumors a fair specimen of tissue may be secured without danger of perforating the bladder wall. The more papillomatous growths with broad bases that are not easily visualized offer more difficulty. Puncture of the bladder with extravasation can easily occur. This is mentioned because of the constant plea for larger and deeper biopsy specimens. If the specimen has been adequate in depth and special attention directed toward it by the pathologist the extent of invasion into the bladder wall at that particular point may be determined Few such specimens are secured and even when they are, too much emphasis must not be placed on the pathological report in the overall estimation of the real degree of invasion and extent of the tumor. Cancer seldom grows symmetrically and penetration may be much deeper at some point outside the biopsy area In fact many of these invasive tumors grow in the plane of the bladder and may extend deep laterally for some distance beyond the bounds of the lesion presenting in the bladder. Graves[6] has expressed our view in this regard: "The adequate preoperative biopsy is not so simple as it sounds and perhaps not so important " One must conclude that the biopsy report is simply one factor to be considered in the final analysis; other findings may be more conclusive

Bimanual rectal or vaginal examination under anesthesia perhaps gives the best index, in most cases, to the extent of invasion of these tumors. If a mass is present in the area around the tumor, its size and degree of mobility will convey to the trained examiner a definite impression of the extent of growth

From the cystoscopic examination, the biopsy report and bimanual examination, one usually can determine with fair degree of accuracy the type of tumor and its degree of penetration. The location of the lesion within the bladder must be considered, whether it is located at the base or above, and whether either ureteral orifice or the urethra is involved or threatened with invasion Evaluation of all these factors is necessary in determining the type of treatment to be applied. Each case must be considered on its individual findings Flocks[7] has stressed this point and urged that the surgeon not attempt to classify cases too sharply into groups and apply treatment as related to the group but rather to fit the therapy to the particular case In the treatment of bladder cancer (the two extreme degrees of malignancy excluded) one must realize that he is to proceed with a considerable degree of doubt as to the actual potentialities and extent of the disease Conjecture or inference gained from one or more elements of the examination may lead to over-emphasis of one and lack of regard for the other.

In the discussion of treatment we would consider bladder tumors in only two broad classes, the benign papilloma and the invasive tumors, whether they be papillomatous or sessile. All seem agreed that the former are to be treated by simple fulguration This is usually done cystoscopically or in some cases of multiple lesions, suprapubically. When multiple, with a tendency to recur in various locations (papillomatosis), x-ray therapy is often used

[6] Graves, R C Discussion of Jewett's paper, J Urol , 67: 677, 1952
[7] Flocks, R H J A M A , 145: 295, 1951

In the treatment of invading carcinoma, whether superficial or advanced, we have relied upon the combination of surgical removal when possible, supplemented by radiation, usually with radon seeds. There is ample evidence that most bladder tumors are radiosensitive. As late as October 1952, Kligerman et al.[2] reported a group of 347 cases, 198 of which were treated by radium alone and 149 by segmental resection. Their conclusion was "A higher percentage of patients with carcinoma of the bladder are clinically free of the disease at any given time following radium implantation than a similar group treated by segmental resection." In support of the ineffectiveness of surgery alone in penetrating tumors, Jewett[8] reports that there were only 3 per cent survivals after 5 years following complete extirpation of the bladder in tumors that had invaded deeply into the bladder wall. This is small hope to hold out to patients upon whom so major a procedure is to be carried out, it being remembered that there is no accurate way to determine exactly preoperatively the extent of invasion. Colby and Kerr[3] state that total cystectomy in their hands gave only 10 per cent 5-year cures if the bladder muscle had been invaded to any extent. The extremely radical cystectomy reported by Victor Marshall[5] has yet to be evaluated. He states that 104 such operations were done in which the entire contents of the pelvis were removed except that in 51 the rectum was left in place. No mortality nor morbidity facts are mentioned. We have seen no patients in whom we have felt that such a procedure was justifiable.

In a series of 95 consecutive cases we found 30 to be simple, noninvasive papilloma. All of these 30 cases were treated by fulguration through the cystoscope except for 3 treated by suprapubic fulguration because of the multiplicity of the growths and their location. None of the patients has died as a result of his bladder tumor.

The remaining 65 showed some evidence of invasion either by pre- or postoperative biopsy study. Twenty-three were found suitable for only palliative treatment. Included are cases in which an exploratory operation was done and too extensive invasion found to warrant attempts to remove the tumor. Also are included a number of senile patients in whom no form of treatment could be carried out.

The remaining 42 cases compose those of invasive carcinoma of all degrees, from the most superficial to those in which the tumor extended deeply into the muscle. These patients were operated upon by several methods: 1) deep fulguration cystoscopically with radon implantation; 2) suprapubic fulguration with radon implantation (largely tumors of the bladder base); 3) segmental resection after fulguration, and radon implantation. In 4 of these in which the ureteral orifice was involved, the ureter was transplanted into another location in the bladder.

There were no primary surgical deaths in this series of 42 patients. Postoperative x-ray treatment was carried out at some period after the operation in the majority of the cases. All the treatment by radiation both by radon and x-ray was done in cooperation with a radiologist.

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[8] Jewett, H. J.: J. A. M. A., **148:** 187, 1952.

Ten of these 45 patients with known invasive type of bladder cancer of varying degrees of extension are known to have lived five years or longer. This is 22 per cent of the 12 cases. This small series is certainly of no value statistically, it is not reported for that purpose. The reason for this discussion is to simply report that in our opinion good results may be secured by conservative methods in treating these patients. We have tried to combine in a rational manner fulguration, open surgery and radiation and believe that these measures properly applied to most cases of invasive bladder cancer will give as favorable results as more radical procedures There is certainly a place for ureterosigmoidostomy in the treatment of these cases particularly as a palliative measure for a few in which diversion of the urine is advisable. It is desirable that those who have opportunity to promote research in radical surgery for bladder tumor continue to do so. There is reason to believe that much progress may be made in this field. Until we have better and more accurate methods of securing adequate biopsies and thereby are able to determine with more certainty the degree of malignancy and extent of invasion, it would seem reasonable that we should lean towards conservative methods of treatment.

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LOCALIZATION OF RADIOACTIVITY IN THE URINARY BLADDER AND THE REGIONAL LYMPH NODES

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Two of the important factors influencing the prognosis of urinary bladder carcinoma are the type of tumor and the depth of invasion into the bladder wall.[1, 2, 3, 4] These carcinomas range from the noninvasive papillary type through the infiltrating transitional cell, or papillary, cancers to the highly lethal squamous cell variety.

The preferred method of treatment for bladder cancer has been the subject of much dispute for two decades. When the tumor is noninvasive, or only superficially invasive, claims of success by all methods of treatment (transurethral resection, subtotal cystectomy, total cystectomy, cystotomy with fulguration and implantation of radium or radon seeds) seem to be about equal. On the other hand, when the tumor has penetrated deeply into, or through, the detrusor urinae, no method of treatment, developed to date, has proved very satisfactory. There has not been a sufficient number of cases treated by the more radical surgical approach and with an adequate follow-up interval to give additional reason for hope in this type of cancer.

An additional important factor in the prognosis of infiltrating bladder cancer is the relatively high incidence of lymph node involvement present at the time of operation.[5] The route of lymphatic spread in the human is principally to the medial and middle groups of external iliac lymph nodes and less frequently to the hypogastric and common iliac nodes.[6] The hypogastric nodes become more frequently involved when the site of the tumor is on the posterior wall of the urinary bladder.

This paper is a report of animal experiments performed with the hope of gaining information which might prove useful in the therapy of invasive carcinomas.

An attempt to develop a method of delivering an effective dose of radiation limited to the region of a urinary bladder tumor and its lymphatic drainage was made. This method consisted of injecting a radioactive colloidal solution into the wall of the urinary bladder. The colloidal particles are apparently phagocytosed and carried through the lymphatic channels to the regional lymph nodes.[7, 8] If

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Read at annual meeting, Southeastern Section of American Urological Association, Havana, Cuba, March 26–29, 1953.

This project was supported by a grant from the Damon Runyon Memorial Fund for Cancer Research.

This work was done under the supervision of Dr. Marshall Brucer, Chairman of the Medical Division of the Oak Ridge Institute of Nuclear Studies. Miss Germaine Click contributed invaluable technical help and advice.

[1] Tuovinen, P. I.: Ann. chir. et gynaec. Fenniae, vol. 37, supp. 5, 1948.

[2] Jewett, H. J.: South. Med. J., **43**: 661, 1950.

[3] Dean, A. L. and Ash, J. E.: J. Urol., **63**: 618, 1950.

[4] Colby, F. H. and Kerr, W. S., Jr.: New Eng. J. Med., **244**: 504, 1951.

[5] Kerr, W. S., Jr. and Colby, F. H.: J. Urol., **63**: 842, 1950.

[6] Ackerman, L. V. and del Regato, J. A.: Cancer Diagnosis, Treatment and Prognosis. St. Louis: C. V. Mosby Co., p. 715.

[7] Flocks, R. H., Kerr, H. D., Elkins, H. B. and Culp, D.: J. Urol., **68**: 610, 1950.

[8] Sherman, A. I., Nolan, J. F. and Allen, W. M.: Am. J. of Roentgenol., **64**: 75, 1950.

the radioactive uptake in the theoretical tumor site and in the lymph nodes is high enough to deliver an effective dose of radiation, a certain amount of palliation should be anticipated.

ISOTOPE

Radioactive colloidal gold^{198} was used. Au^{198} may not necessarily be the ideal isotope for clinical application of this method, but it was chosen because of its availability and short half-life which make it a convenient and desirable laboratory isotope. Au^{198} has a half-life of 2.7 days. It emits beta rays with maximum energy of 0.97 mev. and gamma rays with energy of 0.11 mev. Fifty per cent of the beta rays penetrate only 0.38 mm. and are the primary source of radiation effect. The gamma rays penetrate deeply and are useful for external counting. The isotope, obtained from Abbott Research Laboratory of Oak Ridge, Tennessee, is a colloidal solution of particle sizes stated to range from .003 to .004 microns.

METHOD

Apparently healthy mongrel dogs were used. The dogs were anesthetized with intravenous sodium pentobarbital, 30 mg./kilo weight. Under sterile conditions a lower abdominal midline incision was made, the urinary bladder was exposed and delivered through the wound. A dose of colloidal Au^{198} was then injected into the muscular layer at the fundus of the bladder, using a lead-protected syringe. The bladder was returned to its position and the abdominal wall was closed.

DOSE

Five millicuries of Au^{198} in 5 cc of N. saline to which 300 turbidity units of hyaluronidase had been added, was injected. Hyaluronidase was added because it has been suggested that it would create a uniform dispersion of the solution

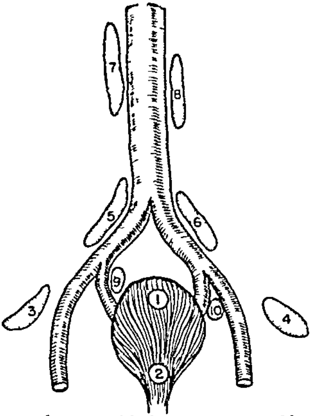

FIG. 1. Schematic diagram of urinary bladder and regional lymph nodes of dog indicating areas of assay.

throughout the muscular wall,[9, 10, 11, 12, 13] and would probably allow a more effective lymphatic pickup.

AUTOPSY AND ASSAY

The dogs were sacrificed at intervals ranging from five to fifteen days after the injection. Specimens taken from various organs and lymph nodes (fig. 1) were examined for radioactive uptake and histologic changes. The tissue was weighed, digested in nitric acid and diluted to 10 cc volume. The activity in this wet sample was measured with an end-window Geiger-Mueller tube. All figures are recorded as the count per minute per gram of fresh tissue corrected for decay from the time of animal injection.

RESULTS OF ASSAY

Twelve dogs were used. The radiation uptake count in the various organs examined is given to table 1. A high concentration was, of course, found at the site of injection in all the dogs. A fairly consistent uptake with surprisingly high levels was found in the lymph nodes draining the urinary bladder. The nodes along the hypogastric artery, when found, showed the highest activity. The iliac nodes and aortic nodes also showed relatively high concentrations. Very low counts were found in the liver and spleen, indicating that only a minimal amount of Au^{198} entered the blood stream.[14] A certain amount of spillage into the peritoneal cavity undoubtedly occurred during each injection. Free colloidal Au^{198} is very rapidly picked up by the reticulo-endothelial cells of the omentum and can explain the consistently elevated concentration of radioactive material found in the omentum of all of the dogs.[15]

The bladder trigone also had a consistently elevated level of radioactivity, despite the fact that the injection site was several centimeters distant. This may be explained by the rich collateral lymphatic plexus of the urinary bladder as well as the dispersing activity of the added hyaluronidase.

PATHOLOGY

The urinary bladders of four dogs examined 5 days after injection all showed considerable thickening of the bladder wall for several centimeters around the site of injection; this was accounted for by edema and congestion. The areas near the injection site showed early necrosis of the muscle with adjacent fibroblastic proliferation in a loose stroma rich in dilated capillaries (fig. 2) with swollen endothelial cells. There was a thin layer of fibrin on the peritoneal surface with stratification of swollen mesothelial cells. With the exception of swelling of the transitional cells, the mucosa was not remarkable.

Seven dogs examined 13 days and one dog 15 days after injection showed

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[9] Hechter, O., Dopkeen, S. K. and Yudell, M. H.: J. Pediat., **30:** 645, 1947.

[10] Schwartzman, J., et. al.: J. Pediat., **33:** 267, 1950.

[11] Schwartzman, J.: J. Pediat., **34:** 559, 1949.

[12] Schwartzman, J. and Levbarg, M.: J. Pediat., **36:** 79, 1950.

[13] Henderson, A T., Wallace, S. L. and Faucett, R. E.: U. S. Nav. Med. Bull., **48:** 865, 1946.

[14] Berg, H. F.: Arch. Surg., **63:** 545, 1951.

[15] Ibid.

TABLE 1. *Radioassay in 12 dogs following injection of radiogold into wall of urinary bladder*

	Dog No	110	109	113	114	81	87	92	99	100	103	101	108
	Amount of Au^{198}	5 mc	5 mc	5 mc	5 mc	5 mc	5 mc	5 mc	5 mc	5 mc	5 mc	5 mc	5 mc
	Time Interval—days	5	5	5	5	13	13	13	13	13	13	13	15
No	Anatomical location												
1	Bladder—fundus	105,100	38,800	72,700	33,000	67,200	54,200	11,100	23,500	21,500	7,200	6,200	95,900
2	Bladder—trigone	59,900	10,600	53,300	370	31,000	760	9,270	1,250	80,600	18,700	11,700	1,290
3	Rt. inguinal L.N.	120	200	15	590	0	*	0	*	365	35	310	0
4	Lt. inguinal L.N.	65	75	140	740	0	60	0	9,340	235	65	80	0
5	Rt. iliac L.N.	5,950	51,600	61,800	8,100	164,000	3,160	10,900	13,190	26,200	22,200	1,210	146,100
6	Lt. iliac L N.	22,000	860,800	21,600	19,800	79,800	131,000	6,320	56,000	94,600	19,800	12,300	2,930
7	Rt. aortic L N.	520	*	371,000	56,200	0	100	31,000	*	*	780	740	58,100
8	Lt. aortic L.N.	1,730	1,890	33,400	0	850	140	19,000	1,290	550	140	1,570	*
9	Rt. hypogastric L.N.	127,300	269,000	*	720	0	*	*	*	*	92,100	370,600	151,100
10	Lt. hypogastric L.N.	121,000	119,000	620	15,600	0	*	*	1,160	*	*	*	10,100
11	Spleen	40	20	30	70	0	0	210	170	210	11,600	0	1,040
12	Lung	1	1	115	90	0	105	0	0	50	290	110	615
13	Heart	0	0	20	15	0	25	0	65	7	150	0	0
14	Liver	65	30	270	100	1,020	100	620	2,020	1,090	700	210	185
15	Kidney	110	10	0	0	30	60	130	60	65	0	215	175
16	Ureter	10	0	16,700	0	0	280	580	1,280	370	*	2,760	0
17	Mesenteric L.N.	*	60	*	110	85	5	310	280	75	240	0	100
18	Omentum	1,225	11,800	2,350	10,800	35,900	580	2,890	5,170	510	2,910	0	15,600
	Background	15	15	16	16	18	15	16	15	15	15	16	16

5 mc. Au^{198} + 300 TR units of hyaluronidase in 5 cc. vol. injected in fundic wall of urinary bladder (dogs) Figures are the count/minute/gram tissue of organ, corrected for decay. 0—Count below background. *—No specimen.

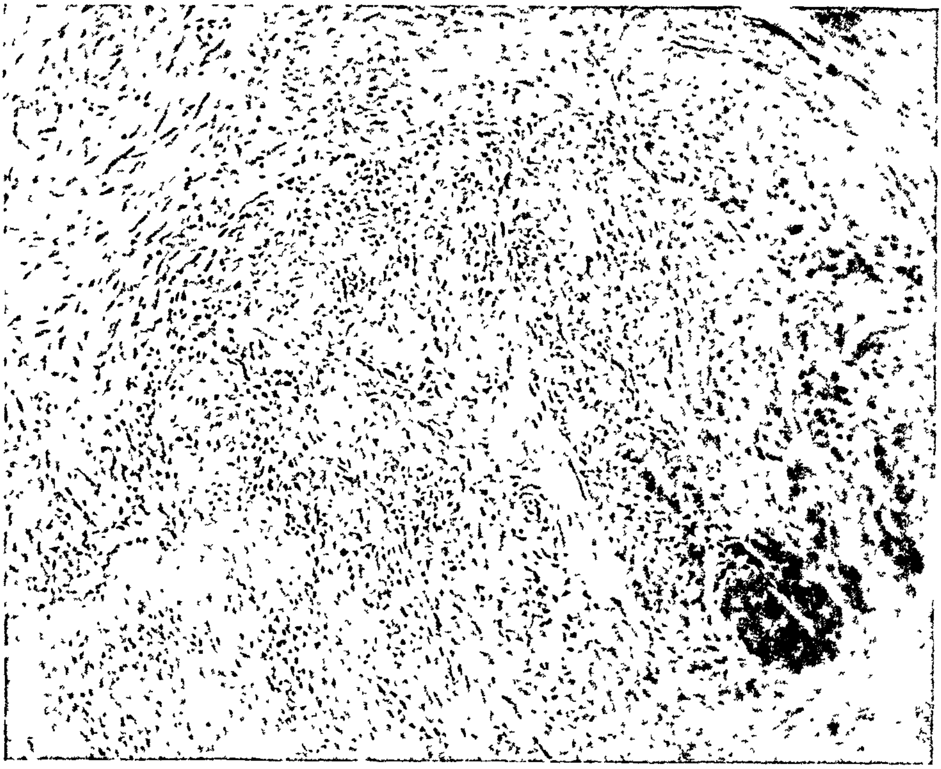

FIG. 2. Photomicrograph of section of urinary bladder (dog 114) injected with Au^{198} showing necrosis of muscle and fibroblastic proliferation.

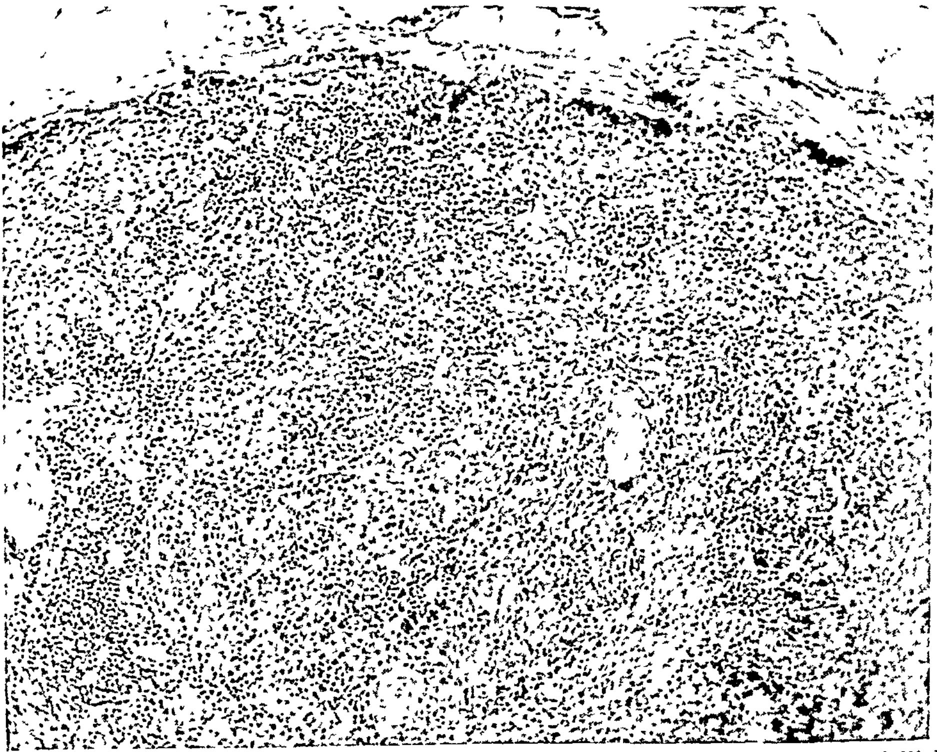

FIG. 3. Photomicrograph of a regional lymph node (dog 100) showing loss of follicles, depletion of lymphocytes, and marked increase in reticulum cells.

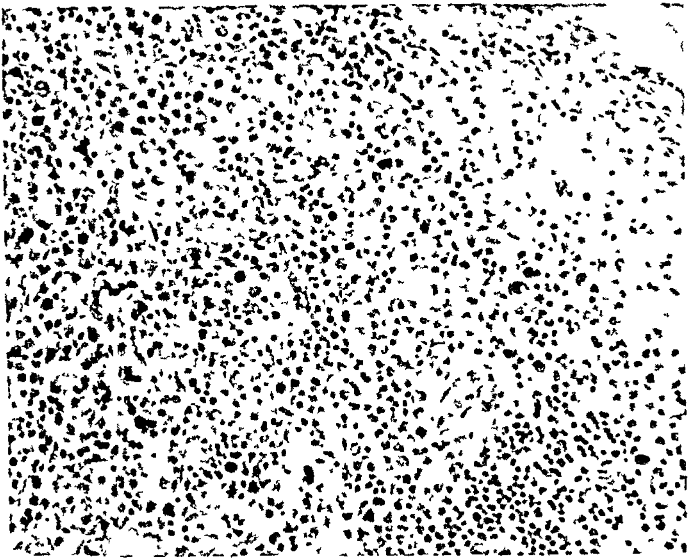

Fig 4 Higher power magnification Note sparsity and pyknosis of lymphocytes increase in reticulum cells *Peripheral sinus is obliterated Capsule can be seen in upper right corner*

changes in the urinary bladder similar to the first group with the exception that there was less fibrin on the peritoneal surface and rather marked fibroblastic proliferation beneath the peritoneum and in the muscle about the injection site There was minimal mixed leukocytic response

The regional lymph nodes in this latter group were small and could not be found in all cases The histologic findings were qualitatively similar but differed *somewhat* quantitatively The peripheral sinus was often packed with large pigment-containing mononuclear cells In scattered foci the sinus was replaced by fibrous tissue rich in these pigmented cells Only an occasional node showed marked fragmentation of lymphocytes Plasma cells often made up from about one-sixth to one fourth of the cellular element Follicles with germinal centers were always present, but were apparently decreased in number often showing only one or two in a cross section (figs 3 and 4) No consistent change in blood vessels was noted

The bone marrow was of normal cellularity without detectable maturation abnormalities

DISCUSSION

The deliverance of effective radiation to an inoperable bladder cancer and the regional nodes by conventional radiation therapy has well-known limitations, particularly the damaging effect on adjacent structures The method used in this experiment seems to accomplish well localized effect on the urinary bladder of dogs. At the same time, appreciable radiation is delivered to the regional lymph nodes and a minimal amount of activity is detectable elsewhere in the body. If a higher level dosage of activity were used, one might expect more necrosis at the injection site and higher concentrations of activity in the lymph nodes.

Direct injection of colloidal Au^{198} into tumors has been done with reported success.[16, 17, 18] The major defect in this method has been the uneven dispersion of the radioactive particles, thus failing to deliver uniform radiation. Results will undoubtedly be improved with the development of better techniques.

It is important to remember that these were healthy dogs without carcinoma. In the event the lymphatics are "plugged" with metastatic emboli, it is quite possible that the localization in the lymph nodes would not be so concentrated, or may not have resulted at all. The only way we know to prove this would be by clinical application and trial.

SUMMARY AND CONCLUSIONS

A colloidal solution of Au^{198} was injected intramurally into the urinary bladder of 12 dogs.

Assay and histologic studies were made on dogs sacrificed at various time intervals ranging from five to fifteen days.

Concentrations of radioactivity were found to be consistently high at the site of injection as well as in the trigone of the urinary bladder and in the regional lymph nodes.

Radiogold produced necrosis of the urinary bladder wall at the site of injection. Minor changes were noted in the regional lymph nodes.

These results suggest the possibility of a clinical trial in patients with inoperable bladder carcinoma. Palliation might be afforded these patients if a sufficiently large amount of isotope were utilized creating an effective radiation dose.

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[16] Hahn, P. F. and Sheppard, C. W.: Ann. Int. Med., **28**: 598, 1948.

[17] Flocks, R. H. et al.: Loc. cit.

[18] Sherman, A. I., Nolan, J. F. and Allen, W. M.: Loc. cit.

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EXTERNAL URETHRAL MEATOTOMY IN THE FEMALE

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External urethral meatotomy in the female is an easy procedure that requires little time, only a few instruments, and gives excellent results. Complications are infrequent and minimal when they do occur. The indication for this procedure is stricture or stenosis of the female external urethral meatus that does not tolerate comfortably a 30F sound. Meatotomy is done by cutting the posterior lip of the meatus at 6 o'clock (on the face of a clock) at the urethrovaginal juncture. An alternate method is to produce a "fishmouth" pair of incisions at 4 and 8 o'clock (on the face of a clock). Either procedure gives good results

The technique (figs. 1 to 3) consists of injecting about ½ cc of 1 per cent novacain with a sharp, short beveled hypodermic needle at 6 o'clock on the circumference of the meatus. Occasionally it is necessary to "iron out" the urethral meatus with a small sound. After the original injection a small amount of novacain is infiltrated quickly along the floor of the urethra at 6 o'clock and at 5 and 7 o'clock. One half to ¾ cc of 1 per cent novocain is sufficient. As soon as a "bleb" has been raised the rest of the procedure is painless practically. After the sound is removed, a straight hemostat is clamped onto the posterior lip of the meatus, and extending into the urethra from 1/16 to 1/8 inch. It is better to do too little than too much, and occasionally a second procedure will be necessary to secure an adequate opening. This hemostat is left on for 30 seconds to give adequate hemostasis. It is then removed gently and a pair of straight scissors

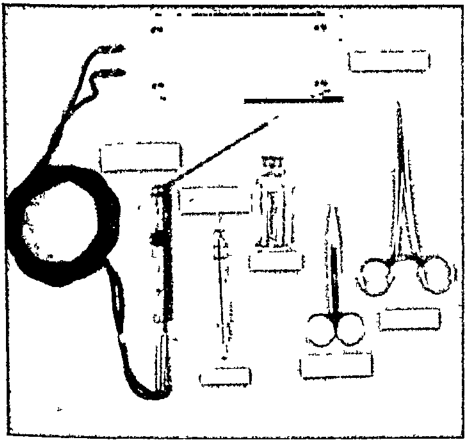

Fig 1 Showing all instruments necessary for procedure

Read at annual meeting, Southeastern Section of American Urological Association, Havana, Cuba, March 26-29, 1953

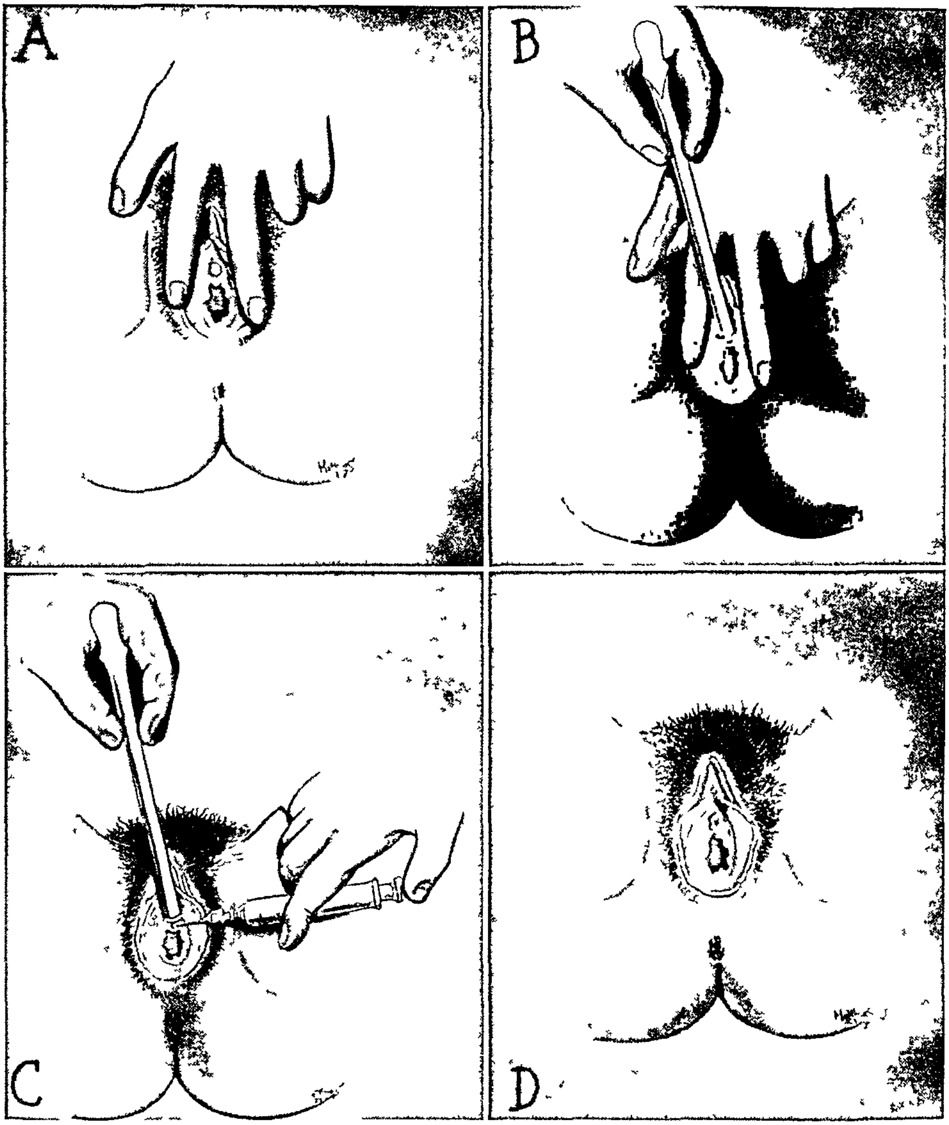

FIG 2 Lithotomy position showing female genitalia and meatal stricture *B*, with a 30F sound inserted through strictured urethra *C*, injection of 1 per cent novocain into posterior lip of meatus *D*, bullous swelling following novocain injection

used to cut along the indentation caused by the hemostat clamping of the tissues. Nos. 24, 26, 28 and 30 sounds are then introduced into the urethra. If there is any "hang" as a sound is passed a small electric cautery tip ("electric needle") is used to enlarge the incision and to secure hemostasis. This is painless provided the steam is not allowed to accumulate around the vulva. An assistant holds the sound while the left forefinger and middle finger of the operator keep the labia apart sufficiently so that no heat or steam can cause discomfort to the patient. Because the small blade used for the electric cautery heats and cools very quickly only a fraction of a second is needed to cut or to coagulate bleeding A 30F sound should pass without any hanging. A small pledget of cotton is inserted

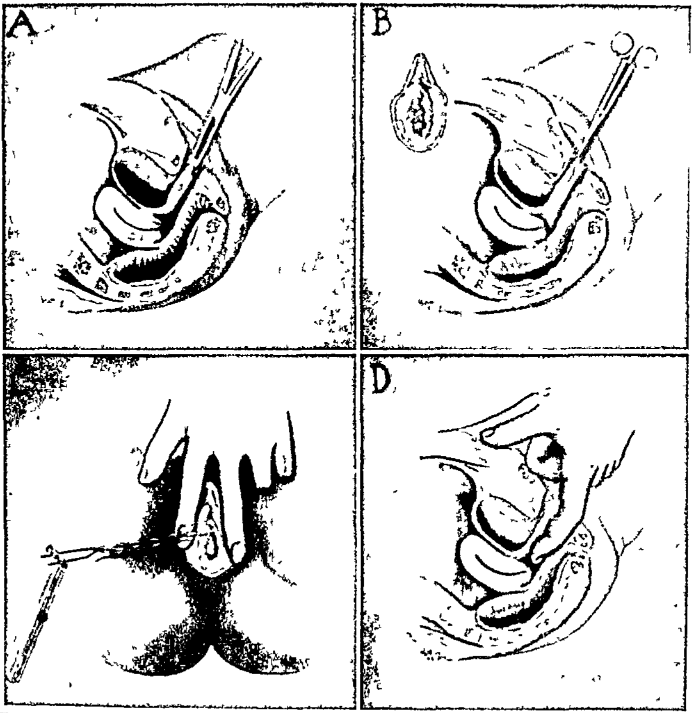

FIG. 3. *A*, sagittal view showing hemostat applied on distal ⅛ inch of posterior lip of meatus *B*, sagittal view showing scissors cutting "clamped" area of posterior lip of meatus. *C*, use of electric cautery tip to control bleeding *D*, sagittal view with finger pressing cotton against cut meatus

into the vagina beneath the cut meatus. The patient is told to remove the cotton before she urinates. If there is any bleeding after urination, she is to re-insert another pledget of cotton and to compress the cotton and meatus against the symphysis by finger pressure. Cotton is kept in as long as there is any bleeding after urination. Some patients will bleed each time they urinate for several days, others will not bleed at all. Still others will have an occasional show of blood and will have to wear a piece of cotton during the next ten days It is possible by this method to control the rare case of hemorrhage that occurs. Sometimes digital compressions of the meatus against the symphysis pubis will be required for a period of three or four minutes before hemostasis is secured. Only twice has the author had to re-inject the area with novocain and fulgurate a particularly troublesome bleeder.

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The microscopic appearance of this type is characterized by reaction without gland formation or with only a tendency to gland formation. In its acute phase, there is moderate to marked edema of transitional mucosa and submucosa, increased vascularity of the mucosa and submucosa with a minimal number of inflammatory cells (fig. 1, *A*). The less acute phase of the granular type shows an increased number of lymphoid elements and less vascularity.

The second type is the acute edematous or the acute polypoid type. This is

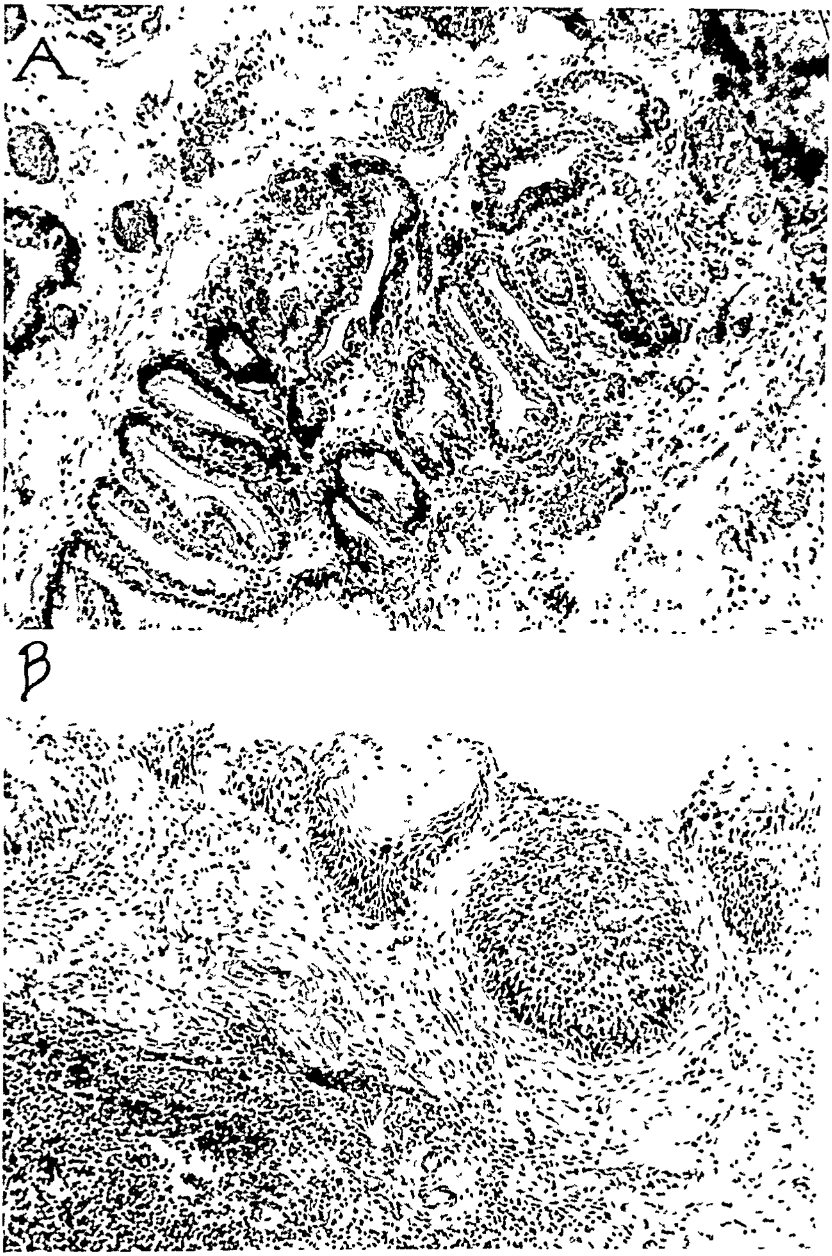

Fig. 2. *A*, section of subacute glandular urethritis showing marked gland formation, increased vascularity with moderate amount of lymphocytic infiltration. *B*, more chronic phase of subacute glandular reaction. Note marked lymphoid reaction, almost gland-like in character, less vascularity, and minimal edema of submucosa.

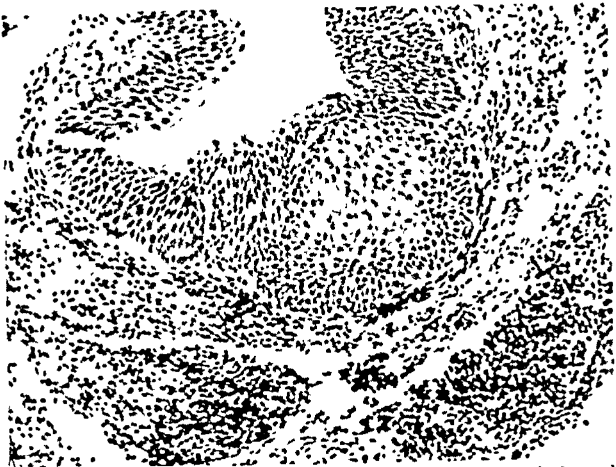

FIG. 3. Section from healed glandular urethritis. Squamous metaplasia and marked lymphoid infiltration are characteristic of type.

a marked inflammatory reaction. Here the mucosa has a polypoid appearance and is diffusely red and edematous. The microscopic section shows marked edema of the mucosa with marked vascularity. Chronic inflammatory elements are absent. Here the glandular structure is evident (fig. 1, *B*).

The third type is the subsiding or subacute change with a polypoid-like appearance, the so-called hyperplastic tab. Here the tab shows a red vascular base with either edema of the tip of the polyps or a complete normal epithelization of it. Some of the tabs are very large, some are only filamentous in appearance.

The microscopic section in this type is characterized by gland formation or pseudo-gland formation where in many instances the lumina are filled with acidophilic mucin. In the more acute reaction there is edema of the mucosa, moderate to severe edema of the submucosa, the vessels of the mucosa are both large and small, and there is a minimal lymphoid infiltration (fig. 2, *A*). The less acute reaction is manifested by less edema and an increase in the amount of lymphocytic infiltration even to the appearance of lymph gland formation (fig. 2, *B*).

The fourth type or the healed stage shows the polypoid structure entirely epithelized with normal-appearing mucosa or abnormally pale mucosa. On section there is seen squamous metaplasia with minimal to no edema of the mucosa and submucosa and a marked lymphoid infiltration with a minimal number of vessels (fig. 3).

RESULTS OF THE STUDY

The 51 patients who were treated locally received dilatation and the gamut of local administration including the following: ¼– 2 per cent $AgNO_3$; ½–5 per cent Protargol; Furacin 1:2 and 1:6 dilution; and a 1 per cent Terramycin solution.

Seventeen cases were classified as granular, and of these only four failed to clear completely as to the appearance of the urethra, symptoms, and recurrences over a 1-year period. This group received an average of 5 treatments per patient, a figure somewhat above the actual average because one patient received a total of 19 treatments. Of the four who failed, one patient had diabetes and one other had chronic pyelonephritis.

Four cases were of the acute glandular type; one cleared completely and the other three subsided with only minimal evidence of the severe reaction after three treatments.

Twenty-eight patients were described as the subacute glandular type. Of this

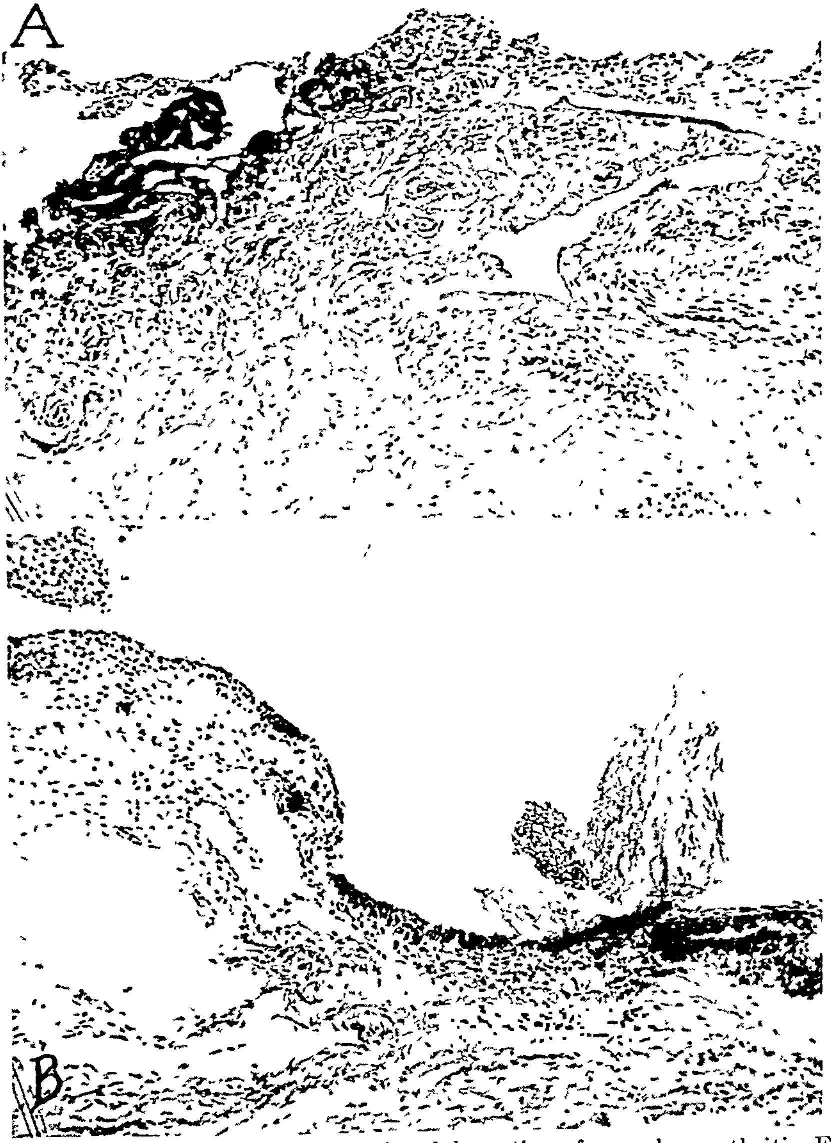

FIG. 4. *A*, section taken immediately after fulguration of granular urethritis. Extensive destruction of tissue is evident. *B*, urethra that had been fulgurated in granular stage 6 months previously.

group, in only 3 cases did the urethra return to normal, and these were described as small filamentous tabs. This group received an average of eight treatments per patient.

Two patients were classified in the healed group. One of these showed no change, the other cleared with local medication and estrogen suppositories.

A detailed endoscopic description of each of the 25 patients on whom biopsies were taken with the pathologist's description of the biopsy was compiled. The conclusions were those reached in the classification, and because it entails seven pages is not included.

Having established the comparison between the endoscopic appearance and the pathological specimen we then wanted to determine what types of responses might be anticipated from the two basic forms of therapy on each of the types of urethritis by taking biopsies immediately after treatment. We used 2 per

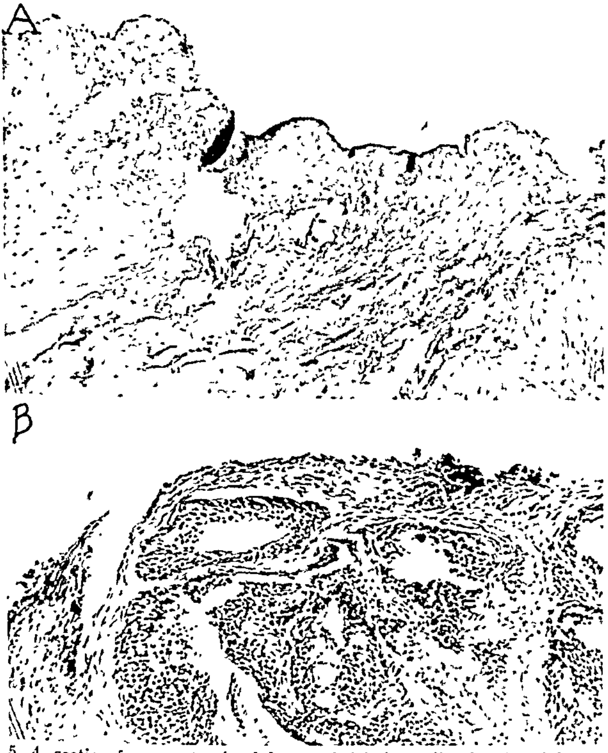

FIG. 5. *A*, section from acute glandular urethritis immediately after fulguration. Extensive destruction again noted. *B*, biopsy after application of 2 per cent silver nitrate on subacute glandular urethritis. Silver stain may be seen over tips of glands.

cent silver nitrate for maximum penetration and staining. The results are included in the discussion.

DISCUSSION

The granular stage shows an increased vascularity with minimal inflammatory cells and no metaplasia but, most important, no glands or only a tendency to form glands. This type responds to almost any form of therapy, drugs in the young and mild local therapy in the older patient. These patients need not be subjected to urethral fulguration. Figure 4, *A* shows a section from a granular urethra after fulguration. One notes destruction of the mucosa and submucosa, leaving only charring and muscle fibers. While the mucosa will eventually return to normal, figure 4, *B* shows granular urethra 6 months after fulguration; the morbidity required is rarely necessary. It is evident also that a local medication can come in contact with the mucosa sufficiently to remove the granular reaction. The acute glandular type is an acute reaction and should be treated as such with antibiotics and mild local therapy. Our clinical experience shows that the majority will clear, but if they persist in the subacute form they then should be treated as such. In figure 5, *A* the excessive destruction caused by fulguration is evident and generally results in more morbidity than necessary for this type of pathological change.

With the subacute glandular reaction the response to local medication is poor due to the obvious difficulty of any medication reaching beyond the tips of the glands. Figure 5, *B* shows sections taken after the application of 2 per cent silver nitrate on a swab revealing that the medication reaches only a small portion of the tissue taken for biopsy. Figure 6 shows the good results by fulguration without extensive destruction of the musculature.

The healed, or chronic, stage with squamous metaplasia and marked infiltra-

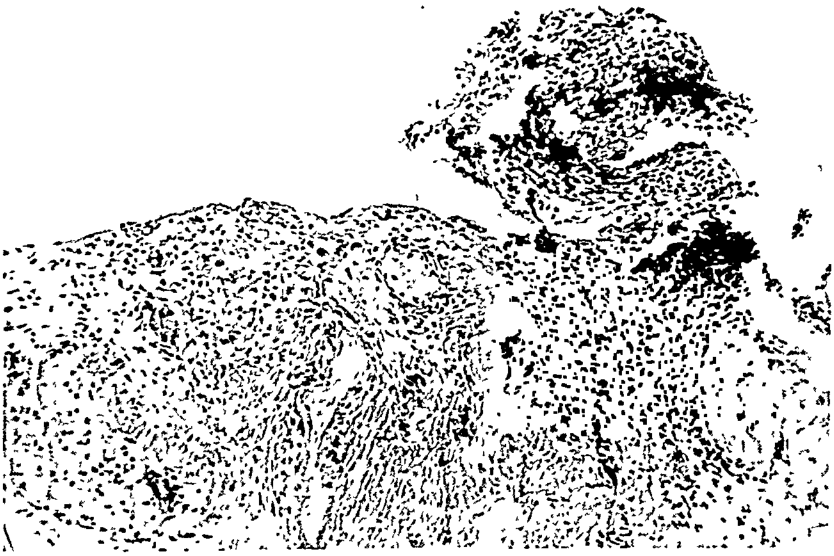

FIG. 6. Post-fulguration biopsy of subacute glandular urethritis showing destruction of glandular elements without extensive destruction of submucosa.

tion of lymphoid tissue usually is resistant to any form of local therapy and is a questionable source of irritation and reflected pains. We feel that patients with this condition should not receive local therapy unless the symptoms per se can be shown definitely to be referred from the urethra[12] and then they should be treated by fulguration or resection

CONCLUSION

Correlation has been shown between the gross appearance of urethritis and the microscopic classification of biopsies taken from the lesion

An adequate number of patients presented show this correlation

The mild reaction and the more severe acute reaction in young women should be treated conservatively by local therapy.

More common are those with large tabs which failed to respond in general to local therapy and who should be treated by fulguration

The chronic, or healed, stage usually being nonamenable to local therapy, should be treated by fulguration or resection.

We want to express our thanks to the Department of Surgical Pathology, Washington University, and particularly to Dr. Vernon Pettit, who reviewed all of our tissue specimens

[12] Powell, E M , and Wattenberg, C A To be published

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PEYRONIE'S DISEASE: CORTISONE-HYALURONIDASE-HYDROCORTISONE THERAPY

HENRY BODNER, ALLAN H. HOWARD AND JOSEPH H. KAPLAN

Since the original description by Peyronie in 1743, the disease which bears his name has been described, variously, as follows: Fibrous cavernositis, fibrous plaques of the penis, chronic cavernositis, fibrous sclerosis and plastic induration of the corpora cavernosa. This preliminary report deals with the results of therapy with adreno-cortical hormones in 16 patients with Peyronie's disease and one additional case in which hyaluronidase alone was used.

The etiology, pathology, symptoms and treatment of Peyronie's disease has been adequately reviewed by Dr. Wesson[1] and by Dr. Burford[2] in the more recent medical literature. We shall, therefore, in this presentation emphasize the therapy in plastic induration of the corpora cavernosa. Wesson stated that "any phallus when turgid or partially so, that has a tendency to be deflected in any part away from a mathematical straight line is a potential case of plastic induration." Pain with erection is a symptom of alarming importance to the average egoistic male. Due to the necessity of frequent daily handling of the penis, the deviation from the normal is readily ascertained. Therefore, curvature of the penis, pain with erection and palpation of the fibrous plaques in the penis are the symptoms of primary importance which stimulate the patient to seek medical aid and are signs and symptoms evaluated before and after therapy.

The treatment of plastic induration of the corpora cavernosa as suggested in the literature has been extremely varied. Topical applications of iodine, mercury, camphor, iodoform; iodides and arsenic internally, massive doses of vitamin E; fibrolysin injected hypodermically into the lesion; diathermy, electrolysis and ultra-violet light; x-ray therapy; radium therapy; surgical excision of the fibrous plaque; and combination of the aforementioned have all been used. It is a foregone conclusion that, in any condition in which a varied number of therapeutic agents are used for therapy, that each method in itself is ineffective in providing a desired result.

Scott[3] in a series of 33 cases reported that slightly over 80 per cent of patients showed at least some response to tocopherol therapy. In Burford's series of 47 cases, 72.4 per cent were either cured or improved by radium therapy. Lowsley concludes that Peyronie's disease is curable by surgery if the plaque formation is not too extensive. He condemns radiation.

This study includes 17 patients and was started in March 1951. There were two patients in the third decade, three patients in the fourth decade, ten patients in the fifth decade and two patients in the sixth decade. The youngest patient was 35 years of age and the oldest 66. In this group of 17 patients, 12 complained

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Read at annual meeting, Western Section of American Urological Association, San Francisco, April 27–30, 1953.

[1] Wesson, M. B.: Peyronie's disease (plastic induration): Cause and treatment. J. Urol., 49: 350–356, 1943.

[2] Burford, C. E., Glenn, J. E. and Burford, E. H.: Fibrous cavernositis: Further observation with report of 31 additional cases. J. Urol., 56: 118–120, 1946.

[3] Scott, William Wallace: Ann. New York Acad. Sc., 52: 390–396, 1949.

TABLE 1 *Results of treatment with cortisone, hydrocortisone, cortisone and hyaluronidase, and hyaluronidase in 17 cases of Peyronie's disease*

DRUG EMPLOYED	NUMBER OF CASES	GOOD	RESULTS IMPROVED	POOR
Cortisone	8	3	5	0
Hydrocortisone	3	1	2	0
Cortisone and hyaluronidase	5	2	2	1
Hyaluronidase	1	0	0	1
Total	17	6	9	2

TABLE 2 *Effect of cortisone, cortisone and hyaluronidase, hydrocortone and hyaluronidase on the curvature of penis produced by Peyronie's disease in 15 cases*

DEGREE OF CURVATURE	NUMBER OF CASES	GOOD	RESULTS IMPROVED	POOR
Mild	6	2	0	4
Moderate	5	1	2	2
Severe	4	2	1	1
Total	15	5	3	7

TABLE 3 *Effect of cortisone, cortisone and hyaluronidase, hydrocortone and hyaluronidase on pain in penis produced by Peyronie's disease in 12 cases*

DEGREE OF PAIN	NUMBER OF CASES	GOOD	RESULTS IMPROVED	POOR
Mild	2	1	1	0
Moderate	6	6	0	0
Severe	4	2	2	0
Total	12	9	3	0

of painful erections and 15 were aware of curvature of the penis during erections A plaque, palpated in all 17 patients, varied in size from about 1½ × 1 cm to involvement of the entire dorsum of the penis Three patients had been treated with alpha tocopherol, two had received x-ray therapy, one diathermy, one radium and one patient had been treated with surgery plus estrogens The patients in this study were divided into the following three groups (tables 1, 2, 3): those treated with cortisone,[4] cortisone and hyaluronidase[5] and hydrocortisone[6] One patient, in addition was treated with hyaluronidase alone A course of therapy arbitrarily consisted of 25 mg of the selected drug once weekly with ½ cc of 1 per cent novocaine for a total of 10 weeks In the 5 patients who received hyaluronidase in addition, 150 turbidity reducing unit dosage was used Upon the completion of one course of therapy, for the following 30 days, the plaque was evaluated from the standpoint of pain, curvature and size. Patients were selected for more than one course of therapy if the plaque or the symptoms it produced were unchanged or only slightly improved. In no instance was more than four courses of therapy given. It was our impression that 25 mg. of cortisone or hydrocortisone given at weekly intervals would not produce any untoward reactions. Six patients had been treated with one course, 8 patients with two courses, one with three courses and 2 patients with four courses of therapy.

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[4] Giles, R G Urol & Cutan Rev, 51 399, 1947

[5] Lowsley, O S and Boyce W H Further experiences with an operation for cure of Peyronie's disease J Urol, 63: 888–899, 1950 Lowsley, O S and Gentile, A J Urol, 57 552, 1947

[6] Baker, Roger, Duncan, Govan and Huffner, J Inhibitory effect of cortisone on strictures of urologic tract Surg, Gynec & Obst, 95: 446–451, 1952

Whenever possible the size of the plaque was measured and recorded. An attempt was made also to evaluate the consistency of the plaque insofar as firmness was concerned, that is, if a plaque felt more pliable after therapy. The duration of the symptoms of these patients when first reporting for care was consistent with that in the literature.

A 10 cc Luer-Lok syringe on a 21 or 22 gauge needle was employed to inject the medication into the plaque. The forefinger and thumb of the left hand grasped the plaque and the needle was then inserted directly into the middle of the lesion. In most instances it was necessary to exert a great deal of pressure on the piston of the syringe to inject the medication into the plaque. On some few occasions it was necessary to begin therapy in the lateral aspect of the plaque, since it was impossible to inject the drugs directly into the lesion. After two or three treatments, less pressure was required for injection.

The results in those treated with cortisone alone were good in three and improved in five. In those treated with cortisone plus hyaluronidase the results were good in two, improved in two and poor in one. In those treated with hydrocortisone the results were good in one and improved in two. The patient treated with hyaluronidase alone showed no change. In the entire series irrespective of the type of medication used, the results are as follows: Good in six, improved in nine and poor in two. One patient treated with hyaluronidase alone stated there was no improvement whatsoever. One patient classified as a failure had marked decrease in pain, but there was no change in the amount of curvature and he was still unable to have intercourse. Therefore, with evaluation from the standpoint of the pain, curvature and size of the plaque, we may conclude that we have demonstrated improvement in 16 out of 17 patients. Of the two patients classified as poor results, one had two courses of therapy and the other had one course of therapy.

Statistics in a small series of cases are inconclusive. However, from preliminary investigation it is apparent that adrenocortical hormones, cortisone and hydrocortisone are effective agents in the treatment of Peyronie's disease. Hydrocortisone is, perhaps, even more effective than cortisone if we may base this conclusion on the results obtained in one case in which the fibrous plaque completely disappeared after three injections of 25 mg. each of hydrocortisone. Hyaluronidase did not effect any change in the size of the plaque in the one case in which it was exclusively used. There were no toxic effects noted in any of the patients included in this study. One-half of the patients in this series had poor response to previous types of therapy. However all of these patients improved on cortisone and hydrocortisone therapy.

It was our impression that the patients who were subjected to three and four courses of therapy invariably demonstrated better results insofar as curvature, pain and the size of the plaques. One cubic centimeter (25 mg.) of hydrocortisone with ½ cc of novocain injected directly into the fibrous plaque for a period of 10 to 40 consecutive weeks is the recommended therapy. Hyaluronidase should also be used.

Further study with a larger number of patients over a longer period of time is warranted.

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TERATOMA TESTIS: REPORT OF 100 CONSECUTIVE CASES

COL. JACK W. SCHWARTZ (MC) AND CAPT. NICHOLAS MALLIS (MC)
From the Urological Section, Letterman Army Hospital, San Francisco, Calif.

This study has been undertaken to evaluate clinically an open series of 100 consecutive malignant tumors of the testicle seen at Letterman Army Hospital between the years 1945 and 1952, inclusive. Testicular tumor presents a much higher incidence of admission in military hospitals than in civilian institutions. During the 8-year period studied, testicular malignancy represented .007 per cent of all admissions to the hospital, 3.5 per cent of all malignancies, and 36 per cent of all malignant urogenital neoplasms.

CLASSIFICATION

Friedman and Moore's[1] pathological classification of teratoma testis has been used in this study. The results are shown in figure 1. Multiple sections were taken of all tumors and when mixed elements were found the tumor was classified under its most malignant character, disregarding the most prevalent cell type. In many cases thorough study of "pure" seminoma has revealed other elements. It is noteworthy that metastatic lesions found at autopsy frequently present a more malignant cell pattern than the primary. The distribution in this series is somewhat at variance with Friedman and Moore's study of 922 cases, embryonal carcinoma representing 48 per cent of our series whereas it was found in only 19 per cent of theirs.

DISTRIBUTION

The average age in the entire series was 28.7 years, the youngest being 16 and the oldest 53 (table 1). All cases occurred in soldiers. The average age of the seminoma patients was slightly higher than in the other groups. The right testis was involved in 56 and the left in 44. One case was bilateral; the second tumor, a teratocarcinoma, developing 6 years after the first which was an embryonal carcinoma. One case occurred in a Negro. The low incidence of this lesion in Negroes was stressed by Merren, Vest and Lupton.[2]

Two tumors occurred in undescended testes and two were found in previously operated cryptorchid testes. The relationship of malignancy to maldescent has been the subject of considerable controversy, but it is our impression that arrested descent is not a predisposing factor in development of testicular tumor. Carroll,[3] in his scholarly statistical study of this subject, concluded that the alleged higher incidence of testicular tumor in cryptorchids cannot be accepted and should not affect the decision for orchiopexy or orchiectomy.

SYMPTOMATOLOGY

There are no pathognomonic symptoms. Painless swelling is the most common symptom. This complaint was presented on admission by 67 patients. The swell-

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[1] Friedman, N. B. and Moore, R. A.: Mil. Surg., **99**: 573, 1946.

[2] Merren, D. D., Vest, S. A. and Lupton, C. H., Jr.: J. Urol., **65**: 128, 1951.

[3] Carroll, W. A.: J. Urol., **61**: 396, 1949.

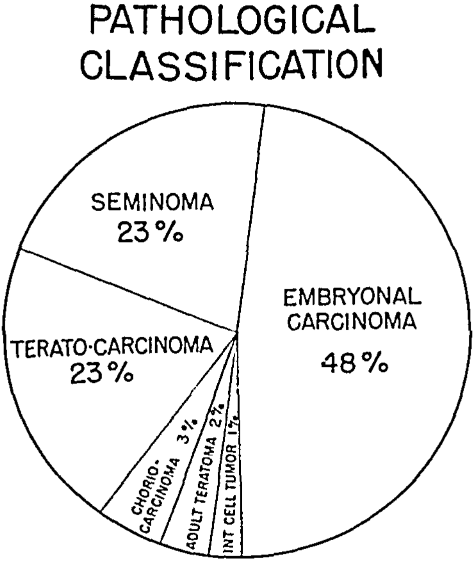

Fig 1

Table 1 *Age distribution*

DIAGNOSIS	AVERAGE AGE IN YEARS	NUMBER BETWEEN 20-30	NUMBER BETWEEN 30-40	MINIMUM AND MAXIMUM
Seminoma	31.2	5	15	19-45
Embryonal carcinoma	29.3	25	21	21-53
Chorio carcinoma	30	1	2	24-30
Terato carcinoma	26	11	6	16-41
Teratoma-adult	30	1	1	28-32
Interstitial-cell tumor	21	1	0	21
Entire group	28.7	47	45	16-53

ing may vary from a tiny irregular nodule to a large firm uniform tumor. The conformation of a tumor does not suggest the histological diagnosis, nor does its size affect the prognosis.

A history of trauma to the involved orchid was elicited from 19 patients. The role of trauma in relation to etiology is uncertain. It may, however, call to the attention of the patient a pre-existing swelling.

The initial symptoms may be associated with metastasis. Six of our patients presented themselves with metastatic symptoms. Gynecomastia should lead one to suspect a hormone producing tumor, and when associated with a testicular neoplasm it is an unfavorable prognostic finding except in the case of interstitial cell tumor. Table 2 lists the presenting symptoms in this series.

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[3] Carroll, W. A.: J. Urol., **61:** 396, 1949.

TABLE 4. *Survival of those showing metastasis on admission*

DIAGNOSIS	TOTAL		ALIVE		DEATHS		LESS 1 YEAR		1-2 YEARS		2-3 YEARS		3-4 YEARS		4-5 YEARS		OVER 5 YEARS	
	No	%	No	%	No	%	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
Seminoma. . .	8	35	8	100	0	0	4	0	0	0	1	0	1	0	1	0	1	0
Embryonal carcinoma . .	17	35	6	35	11	65	1	7	1	4	0	0	0	0	0	0	4	0
Chorio-carcinoma . .	2	67	0	0	2	100	0	2	0	0	0	0	0	0	0	0	0	0
Terato-carcinoma. . . .	11	48	7	64	4	36	3	2	1	2	2	0	0	0	0	0	1	0
Teratoma—adult .	1	50	0	0	1	100	0	1	0	0	0	0	0	0	0	0	0	0
Interstitial-cell tumor	0	0																
Total	39	39	21	54	18	46	8	12	2	6	3	0	1	0	1	0	6	0

site of transection. Eight seminomas, 11 teratocarcinomas, 17 embryonal carcinomas, 2 choriocarcinomas and one adult teratoma comprised this group.

Of the 61 patients who were free of demonstrable metastasis on admission, 26 later developed metastasis after treatment. Of this number 23 are known to be dead. Inguinal and femoral node metastasis occurred in only one case, that in a surgically corrected cryptorchid with extension of the tumor to the scrotal tissues.

Metastasis occurs by way of the lymphatics as a general rule, to the periaortic, mediastinal and supraclavicular nodes. Choriocarcinoma usually spreads by blood stream invasion. Pulmonary metastases are common but other visceral spread occurs only infrequently except as a terminal manifestation. Bony metastases are uncommon.

SURVIVAL

The patients in this series have been followed from 1 month to 8 years. Three have been lost to follow-up. Of the remainder 60 are alive, but 5 of these, one teratocarcinoma and 4 embryonal carcinomas, have metastasis. Thirty-eight patients are alive and well 2 years after treatment, and 24 over 5 years. Of the 60 living patients, 21 had metastasis on admission (table 4). Of the 37 who died, 30 or 81 per cent succumbed within the first 2 years. Metastasis developed in 26 who were free of metastasis on admission, and only three of this group are now alive, one 7 years, one 20 months, and the third 11 months. The last is at present hospitalized with extensive metastasis.

Survival is much higher with seminoma, 90 per cent of our cases being alive. The survival rates of embryonal carcinoma and teratocarcinoma are 44 per cent and 48 per cent respectively in this series. The 3 cases of choriocarcinoma died within 6 months. One of the 2 adult teratomas died within one year with autopsy findings of choriocarcinoma; the other is alive and well over 5 years (tables 5 and 6).

TABLE 5. *Total dead*

DIAGNOSIS	DEATHS		DIED LESS 1 YR.		DIED IN 1-2 YRS		DIED IN 2-3 YRS		DIED IN 3-4 YRS		DIED IN 4-5 YRS		DIED AFTER 5 YRS	
	No	%	No	%	No	%	No.	%	No.	%	No	%	No	%
Seminoma	2	10	0	0	1	50	0	0	1	50	0	0	0	0
Embryonal carcinoma	20	44	9	45	7	35	3	15	1	5	0	0	0	0
Chorio-carcinoma	3	100	3	100	0	0	0	0	0	0	0	0	0	0
Terato-carcinoma	11	48	3	27	6	55	1	9	1	9	0	0	0	0
Teratoma—adult	1	50	1	100	0	0	0	0	0	0	0	0	0	0
Interstitial-cell tumor	0	0												
Total	37	38	16	43	14	38	4	11	3	8	0	0	0	0

TABLE 6. *Overall survival*

DIAGNOSIS	ALIVE		DEATHS		ALIVE c̄ METASTASIS	ALIVE LESS 1 YR	ALIVE 1-2 YRS	ALIVE 2-3 YRS	ALIVE 3-4 YRS.	ALIVE 4-5 YRS	ALIVE OVER 5 YRS.	NOT FOLLOWED
	No	%	No	%								
Seminoma	20	90	2	10	0	4	3	4	3	3	3	1
Embryonal carcinoma	26	56	20	44	4	3	3	0	0	1	19	2
Chorio-carcinoma	0	0	3	100								0
Terato-carcinoma	12	52	11	48	1	7	1	2	0	1	1	0
Teratoma—adult	1	50	1	50	0						1	0
Interstitial-cell tumor	1	100	0	0			1					
Total	60	62	37	38	5	14	8	6	3	5	24	3

Of the 8 patients undergoing retroperitoneal node dissection, five had positive nodes. Of these five all are alive, two with extensive metastasis at this time. Two of those living were seminomas. The fifth, a teratocarcinoma, has been followed less than a year since operation. Of the three with negative nodes, two, both seminomas, are dead from later metastasis. All 8 patients received postoperative radiation.

Our overall survival rate of 62 per cent is relatively high, but 22 of the living cases, five showing metastasis at this time, have been followed less than 2 years.

TREATMENT

Ninety cases were treated by simple orchiectomy and postoperative radiation. Orchiectomy is performed by ligation and transection of the cord in the inguinal canal at the level of the internal ring with delivery of the testis through the inguinal wound. Eight patients had the Chevassu operation, all eight receiving postoperative radiation. Two patients were admitted in a terminal state and received no therapy. No patient received preoperative radiation.

The histological classification of a testicular tumor and the location and extent of metastases are of vital importance in planning a course of radiation therapy and in predicting the probable results of such treatment.

Pure seminoma (probably rare) with limited involvement of lymph nodes along the iliac arteries and aorta is most amenable to radiation treatment, and excellent results may be expected in a high percentage of cases. The seminoma, although histologically undifferentiated and anaplastic has a relatively long natural history and is the most sensitive of the tumors of the testis. It is believed that a tissue dose of 1000r administered in 2 weeks' time is lethal to the cells of pure seminoma; however, in order to insure a better margin of safety the tumor dose should probably never be less than 2000r in 3–4 weeks.

Malignant tumors of the testis, other than seminoma, are more resistant to radiation. The lethal dose for these tumors is estimated to be 4000r or more. This approaches the tolerance of surrounding normal tissue, and serious post-irradiation effects can be anticipated if that dosage, given in a period of 3–4 weeks, is exceeded.

When metastases are confined to the retroperitoneal lymph nodes below the level of the renal pedicles, a course of irradiation in which a tumor dose of 2500–3000r (2000r in seminoma) is delivered through anterior and posterior opposing fields in a period of 3–4 weeks may be considered satisfactory treatment. When metastases are known to be in nodes at the level of the renal pedicles the question of prophylactic treatment of the mediastinum and left sternoclavicular region arises. The general condition of patients who have received a full course of radiation treatment to the retroperitoneal lymph nodes is occasionally such that they cannot very well tolerate a full course of treatment to the mediastinum and the decision is frequently made to treat only the left sternoclavicular area initially and the mediastinum at a later date. Rarely does a patient with mediastinal lymph node involvement survive very long in spite of heavy doses of radiation. The exceptions, however, make the effort worthwhile.

In calculating tumor dosages to the retroperitoneal nodes along the aorta and iliac arteries, it must be remembered that they lie at varying depths from the surface of the abdomen and/or back. Adequate, but not excessive, dosages must be delivered to the nodes at each level.

X-rays in the supervoltage range (1000 KV) offer some advantage over radiations produced at 250 KV in that tumor doses may be delivered in a shorter period of time without increasing the danger to skin and other normal tissue.

TREATMENT OF LATE METASTASES

Metastases which develop after treatment are usually resistant to all types of therapy. Some palliation may be obtained with radiation. Two cases, both teratocarcinoma, were treated by lobectomy for removal of a solitary pulmonary metastasis. One of these patients is alive 32 months since this operation with no other evidence of metastasis.

In two patients with extensive metastasis the opposite normal testis was removed because of favorable response with this procedure reported by Shivers,[5]

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[5] Shivers, C. H. deT.: J. Urol., 54: 539, 1945.

McClelland,[6] Saleely,[7] and others,[8] but in neither instance was the fatal outcome delayed.

Nitrogen mustard, ACTH, cortisone and estrogens, have all been used in terminal cases with equivocal results in some patients and none has shown more than temporary improvement.

COMMENTS

It is our belief that routine retroperitoneal node dissection in testicular tumor has not materially altered the survival rates. When one considers the high incidence of contralateral node involvement, the technical difficulty of exposing the "critical area" in the region of the renal pedicles without relying on heroic incisions, and the likelihood of pre-existing embolic seeding of mediastinal and supraclavicular nodes, the justification for subjecting patients to the ordeals of such a major surgical procedure seems hardly warranted. As a policy, we recommend the Chevassu operation only when cord structures histologically show tumor invasion without evidence of any other metastases and when the tumor type is other than seminoma, interstitial cell tumor or choriocarcinoma. All tumors are postoperatively radiated except the rare interstitial cell tumor which is clinically benign.

The critical period in testicular tumors is the first two years. Well over 90 per cent surviving this period are "cured." The demonstration of metastasis on admission does not necessarily offer a hopeless prognosis. Of our 39 cases fitting this description, 21 are alive, 11 over 5 years. Conversely, metastasis appearing after treatment offers a very serious outlook, 23 of our 26 patients in that category having died within 2 years.

The major hope of reducing the high mortality of this tumor lies not in more refined surgical techniques or in more powerful radiation devices, but in earlier recognition of the lesion.

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[6] Mc Clelland, J. C.: J. Urol., 49: 31, 1943.
[7] Saleely, E. R.: Ann. Surg., 119: 262, 1944.
[8] Wesson, M. B.: Tr. Am. Ass. G-U Surg. 32: 347–358, 1939.

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TUMORS OF THE TESTIS: ANALYSIS OF 80 CASES

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Cancer is a challenge not only to the physician and the surgeon, but also to the scientist. The problem is still shrouded in many mysteries. New theories, as yet immature, may enable us to penetrate the fog. Atomic research has provided a fresh approach to diagnosis and treatment of cancer; it may even lead to unveiling its cause.

Advances in diagnosis and treatment of cancer depend not only on laboratory investigations, but also on clinical corroboration of their applicability and utility. The amount, as well as the diversity, of cancer research under way in this country is so extensive that it is difficult for not only the layman but also the medical man to comprehend.

CLASSIFICATION

The classification of testicular tumors proposed by Moore and Friedman now is widely accepted. Recent embryologic and pathologic observations of testicular tumors as to derivation, character and cellular structure have clarified their origin and behavior, permitting greater specificity in therapy.

ORIGIN

Moore and Friedman compare the formation of testicular tumors to the development of placental and fetal tissue: From the primordial germ cell, after fertilization, there derive the placenta (trophoblastic) and the fetus (somatic); in the case of a testicular tumor, a transition into a seminoma may occur or, through an intermediary stage of embryonal carcinoma, a chorio-epithelioma or teratoma may be formed—but any combination of these phases may materialize.

ANALYSIS OF 80 CASES OF TESTICULAR TUMOR

A series of 80 patients with tumor of the testis is reported here. Data recorded are compared with that in similar series reported by others. These patients were observed at the Wadsworth General Medical and Surgical Hospital in Los Angeles during the period 1946 to 1950 inclusive. A number of additional cases were recorded at this institution during that period but were excluded from the analysis. Several patients, seen by the Tumor Board and given roentgenologic therapy at this unit, had received surgical therapy elsewhere, and the limited clinical, diagnostic and therapeutic data obtained did not lend itself to detailed or critical analysis. Approximately half of the series had been treated surgically and had received some therapy at other hospitals.

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TABLE 1. *Incidence of testicular tumors in series of 80 patients in relation to average expectancy*

	AVERAGE EXPECTANCY (PER CENT)	INCIDENCE IN SERIES (PER CENT)
Seminoma	35	48.75 (includes 5 cases with minor allied types malignancy)
Embryonal carcinoma	19	26.25 (includes 3 cases with allied malignancy)
Teratocarcinoma	35	20.00 (includes 2 cases with chorio-epithelioma)
Teratoma	7	—
Miscellaneous	3	5.00
Interstitial	1	—

TABLE 2. *Incidence classified as to age of patient and type of testicular tumor*

	20 OR LESS	21–30	31–40	41–50	51–60	61–70	71 OR MORE	TYPE TOTAL
Seminoma	1	11	10	8	4			34
Seminoma & embryonal carcinoma		4						4
Seminoma & teratoma		1						1
Embryonal carcinoma		9	6	1	2			18
Embryonal carcinoma & chorio-epithelioma		2	1					3
Teratocarcinoma		8	5	1				14
Teratocarcinoma & chorio-epithelioma		1	1					2
Lymphosarcoma			1					1
Leiomyosarcoma			1					1
Reticulum cell sarcoma						1	1	2
Age Group Total	1	36	25	10	6	1	1	80

Seventy-seven were Caucasian; there was only one Negro in the group. Most were married or had been married. Their average age was 34, slightly lower than in similar series reported by others.

The incidence of seminoma and embryonal carcinoma was higher than the average expectancy, while that of teratocarcinoma was lower; there were no adult teratomas (table 1). Lone chorio-epitheliomas and interstitial cell types of growth were not found. The types of tumor recorded at different age levels are given in table 2. Almost half of the patients were aged 21 to 30; the next most frequent age bracket was 31 to 40. In the patients aged 41 to 60 the majority of tumors were seminomatous. Only 2 patients were older than 60; both had reticulum cell sarcoma. There was a slight preponderance of right-sided neoplasms, 53 per cent. One lymphosarcoma was bilateral.

ETIOLOGY

Trauma. Although trauma was mentioned by 27 per cent of Lewis's patients with testicular tumor, he was of the opinion that trauma probably was not of

TABLE 3. *Previous operations*

	NUMBER PATIENTS	
Herniorrhaphy (total)		5
Ipsilateral (1 patient had three such repairs)	3	
Bilateral	2	
Orchiopexy, ipsilateral		3
Vasoligation, bilateral		1
Total		9

etiologic significance. The possibility that trauma might be an exciting factor prompted us to re-examine the historical data in our series: Seventeen and a half per cent had a history of direct or indirect trauma. The interval between actual injury and initial symptoms averaged 43 months, the shortest being one week, and the longest 11 years. Whether or not previous operative procedures (table 3) might have been a contributing factor from the standpoint of trauma also was considered, but such a relation was not revealed, excluding the traumatic factor incident to orchiopexy.

Cryptorchism. Malignant change in undescended testes was recorded in 11 per cent of 7000 cases reviewed by Gilbert and Hamilton. A history of cryptorchism was determined in 10 of our patients (12.5 per cent). There was unilateral cryptochism with ipsilateral tumor in 8 patients and bilateral cryptorchism with a unilateral tumor in 2 (table 4). Three patients with unilateral masses had undergone orchiopexy. One, in whom orchiopexy had been done 10 years previously, had a mass in the right pelvic region that proved to be seminomatous, although evidence of tumor was not found in the atrophic testis on the right side. This probably exemplifies Friedman's contention that a primary testicular tumor may produce recognizable metastases and then disappear entirely, so that only remnants of scar tissue exist in the testis, the original tumor having completely regressed.

Other factors. The possible significance of orchitis, epididymitis, and other diseases to testicular tumors was investigated, but valid associations could not be deduced. Other malignant lesions were found in only 2 patients (table 5). Familial carcinomatous traits were not revealed in the histories of our patients, and only 1 instance of cryptorchism in a relative was disclosed.

TABLE 4. *Cryptorchism*

	NUMBER PATIENTS	PER CENT TOTAL SERIES
Unilateral cryptorchism with ipsilateral tumor	8	10.0
Bilateral cryptorchism with unilateral tumor (1 patient had spontaneous descent at age 14)	2	2.5
Total	10	12.5

TABLE 5. *Possible predisposing factors*

	NUMBER PATIENTS		
Local inflammatory lesions, total			22
Mumps orchitis (20 patients had history of mumps without orchitis)		5	
Ipsilateral	2		
Contralateral	2		
Bilateral	1		
Epididymitis:		5	
Ipsilateral	3		
Lateralization (?)	2		
Urethritis:		12	
Gonorrheal	10		
Nonspecific	2		
Local noninflammatory lesions, total			5
Hydrocele, ipsilateral	5		
Syphilis			4
Tuberculosis, pulmonary and rectal			2
Malignant lesions:			2
Fibrosarcoma, wrist	1		
Lymphosarcoma, axilla	1		
Total			35

COMPLAINTS

The intervals between onset of symptoms and examination and between symptoms and surgical intervention are given in table 6. The shortest lapse between symptoms and examination was 2 days and the longest 13 years, while the average in 75 patients was almost ten months. The shortest period between onset of symptoms and operation was ten days and the longest thirteen years; the average in 74 patients was eleven and a half months. Such "averages" are not, in themselves, particularly significant, but in 74 patients the individual periods of delay between examination and surgical intervention totalled one hundred and eleven months—or about a month and a half to each case.

Surprisingly, in 16 patients (20 per cent) the initial complaint was not referable to the testis or to the scrotum (table 7). A painful nodule or swelling of the testis

TABLE 6. *Delay in examinations and operations*

Interval between onset of symptoms and examination:		
Shortest period	2 days	
Longest period	13 years	
Average in 75 patients (not known in 5)		9.9 months
Interval between onset of symptoms and operation:		
Shortest period	10 days	
Longest period	13 years	
Average in 74 patients (not known in 6)		11.5 months
Average interval between examination and operation		1.6 months

TABLE 7. *Initial complaints*

	NUMBER PATIENTS	
Localized to scrotum or testis		64
Swelling or nodules, painless	52	
Swelling or nodules, painful	12	
Other complaints		15
Abdominal mass and pain	8	
Fatigue, paresthesia of legs, vomiting	1	
Vomiting, epigastric pain, hemoptysis	1	
Pain, right lower quadrant	1	
Pain, left flank	1	
Pain, right inguinal region	1	
Swelling, left side of neck	1	
Swelling, right side of neck	1	
Not recorded		1
Total		80

was present in 12 (15 per cent). In 8 (10 per cent) there was an abdominal mass.

One patient complained of an abdominal mass of 4 months' duration. Sixteen months previously biopsy of an axillary node had been reported as lymphosarcoma. Apparent regression followed radiation therapy. On admission to this hospital, in addition to the abdominal mass, he was found to have a hard, nodular left testis and roentgenologic evidence of hilar adenopathy. Diagnosis of abdominal lymphosarcoma with metastases to the chest and testis was entered; however, biopsy of the testis was reported as "seminoma." The patient died in a month. All organs and nodes were seats of seminomatous processes, there being no evidence of lymphosarcoma. Nevertheless, review of the initial axillary node biopsy by our pathologists corroborated the original diagnosis of lymphosarcoma.

DIAGNOSIS

Physical examination. Every physician should be aware of certain diagnostic features of testicular tumor, since percentage of cure is as closely related to early diagnosis as to proper treatment.

Physical examination of every patient, whether normal or ill, should include careful inspection of the genitalia. A hard, heavy, nontender, nontransilluminating, unilateral scrotal mass of any size in a young adult is presumptive evidence of a neoplasm, although the older age groups are not exempt. Vague abdominal symptoms, or abdominal or cervical masses in a young man may point to a testicular tumor. Symptoms of obstruction of the upper urinary tract, particularly if unilateral, may stem from a tumor of the testis. The presence of hydrocele in a young male patient should arouse one's suspicions as to possible associated neoplasia. Gray and his co-workers at the Mayo Clinic reported this lesion in 8.7 per cent of their series of tumors of the testis. Seven per cent of our patients had hydrocele.

TABLE 8. *Clinical corroboration of hormonal assays in 80 patients*

	NUMBER TESTS	TESTS CONFIRMED CLINICALLY (PER CENT)
Prolan A	31	75
Friedman or Aschheim-Zondek	36	80
Pregnandiol	23	70
Average clinical corroboration		75

Gynecomastia may be caused by feminizing tumors and chorio-epithelioma. However, of our 7 patients with ipsilateral and bilateral symptoms referable to the breast or nipple, only 2 had associated chorio-epithelioma.

Melicow described the sign of the vas as a helpful differential diagnostic point during the physical examination. When inflammatory lesions are present in the scrotum, the vas becomes considerably thickened and irregular; in neoplasm it tends to remain uninvolved.

When either the cause or the character of a scrotal mass is in doubt, we believe that surgical exploration is mandatory—to determine definitely whether a tumor is present.

Isotopes. Roswit and his colleagues commented on their experience with radioactive phosphorus (P^{32}) in the diagnosis of testicular tumors. Our isotope laboratory group is investigating this method of diagnosis. We are hopeful that other radioactive substances may be used with more success.

Gonadotrophins. All evidence, both experimental and clinical, indicates that chorionic gonadotrophin is elaborated by chorionic tissue and that embryonic tissues *per se* do not produce it; furthermore, no other tissues are known to produce this hormone. Chorionic gonadotrophin, when present in the urine of a patient with a testicular tumor, is identical with that found in the urine of pregnant women. In testicular choriocarcinoma the hormone is produced by the trophoblastic tissue of the tumor.

Our results of hormonal assays are encouraging, as shown in table 8. In nearly equal series of tests on all types of tumors the results proved to be 75 per cent correct, as corroborated by all but postmortem observations. When we added to clinical data the facts secured by detailed postmortem studies in 15 cases, the

TABLE 9. *Postmortem corroboration of hormonal assays and seroflocculation tests in 15 patients*

	NUMBER TESTS	POSTMORTEM CONFIRMATION OF TESTS (PER CENT)
Prolan A	10	80
Friedman or Aschheim-Zondek	10	80
Pregnandiol	9	88
Seroflocculation	10	90
Average postmortem corroboration		84.5

TABLE 10. *Roentgenologic evidence of metastases*

	NUMBER PATIENTS		
Pulmonary			23
Preoperative		5	
Postoperative		11	
Preoperative and postoperative		6	
No operation		1	
Osseous (roentgenograms of spine were negative in 1 case in which metastases found at autopsy)			0
Upper urinary			16
Hydronephrosis		9	
Ipsilateral	7		
Contralateral	1		
Bilateral	1		
Deflection of ureter:			
Ipsilateral	4		
Contralateral	3		
Total			39

TABLE 11. *Diagnoses on admission*

	NUMBER PATIENTS		
Local			60
Testicular tumor		48	
Inflammatory lesions		6	
Acute epididymitis and orchitis	1		
Acute orchitis, nonvenereal	1		
Chronic hypertrophic orchitis	1		
Chronic epididymitis	1		
Tuberculosis of testis (?)	2		
Noninflammatory lesions		6	
Hydrocele	4		
Spermatocele	1		
Inguinal hernia with hydrocele		1	
Abdominal			3
Abdominal tumor, unspecified		1	
Acute appendicitis		1	
Hepatitis		1	
Other			4
Hodgkin's disease or thyroid adenoma		1	
Carcinoma of thyroid		1	
Pyonephrosis, left		1	
Secondary anemia		1	
Not recorded			13
Total			80

TABLE 12. *Extrascrotal masses on admission*

	NUMBER PATIENTS
Supraclavicular (ipsilateral)	2
Abdominal	15
Inguinal (ipsilateral)	1
None	62
Total	80

TABLE 13. *Preoperative diagnoses*

	NUMBER PATIENTS	
Testicular		60
Testicular tumor	53	
Scrotal mass, left	1	
Epididymitis and orchitis	1	
Orchitis, acute, nonvenereal	1	
Tuberculosis, scrotal	1	
Hydrocele	1	
Spermatocele	1	
Torsion of testis	1	
Extratesticular		5
Hodgkin's disease	1	
Metastatic carcinoma, abdomen	1	
Acute appendicitis	1	
Pyonephrosis	1	
Hernia, inguinal, and hydrocele	1	
Not recorded		15
Total		80

percentage of corroboration of the hormonal assays arose to 85 per cent (table 9). Therefore, we are continuing to employ biochemical assays in our study of testicular neoplasms. Hall reported the value of a seroflocculation reaction in cancer. It was positive in 90 per cent of our group of testicular tumors. This test may be a means of diagnosing occult lesions in the testes. We are continuing its use in our present series of patients treated by more radical surgical intervention.

Pyelo-ureterograms disclosed hydronephrosis in 9 cases; 7 ipsilateral, 1 contralateral and 1 bilateral. Deflection of the ureter occurred on the same side in 4 instances and on the opposite side in 3 (table 10).

Roentgenologic bone surveys for metastases were not of diagnostic significance in this series; at postmortem examination 9 instances of bony involvement were

TABLE 14. *Agreement of clinical, operative gross and pathologic diagnoses*

	AGREED	DISAGREED
Clinical and operative gross	41	12
Clinical and pathologic	61	7
Operative gross and pathologic	48	4

TABLE 15. *Method of orchiectomy and where performed*

Method of Orchiectomy:	
High inguinal	33
Low inguinal	6
High scrotal	2
Scrotal (Secondary resection of cord for suspected tumor—not found—done in 2 cases)	32
Abdominal exploration	4
Abdominal	1
Biopsy of testis	1
None	1
Total	80
Where Performed:	
Wadsworth General Medical and Surgical Hospital, Los Angeles	41
Elsewhere	39
Total	80

observed. Surprisingly, in only 48 cases (60 per cent) was "testicular tumor" diagnosed on admission. Furthermore, in 21 cases (26 per cent) the admission diagnosis was not related primarily to the testis (table 11).

Metastases to other organs and tissues may reveal the existence of a tumor of the testis before the local condition is even suspected. In some cases, even after positive biopsy of an extratesticular mass, careful palpation of the genitalia fails to disclose a lesion. If the mass is unilateral, exploration and even partial bivalving of the testis is definitely indicated to establish the diagnosis. In a patient in whom this was not done, autopsy revealed a minute tumor of the testis on the ipsilateral side of a retroperitoneal mass.

Extrascrotal masses (table 12) that eventually were determined to be metastases from the testicular lesion were recorded on admission in 18 patients (22.5 per cent). During physical examination of these men the attention of the examiner may well have been diverted from the local focus of the disease.

Preoperative diagnoses. Testicular tumor was the preoperative diagnosis in only 53 of the 80 cases (66 per cent) (table 13). The urgent necessity for surgical exploration of scrotal masses is thus emphasized. A comparison of clinical, operative gross, and pathologic diagnoses is given in table 14.

TREATMENT

During the last year and a half we have used relatively more extensive surgical therapy for malignant tumors of the testis. In the present communication we evaluate the results of less radical treatment—orchiectomy and radiation—employed during the five-year period 1946 to 1950.

In 39 instances orchiectomy was done through an inguinal incision, the method of choice on our service (table 15). The entire cord, up to the internal ring, was removed; this approach involves minimal handling of the testis until occlusion of the vascular pedicle and lymph channels is accomplished.

TABLE 16. *Roentgenologic therapy*

	AVERAGE INCLUSIVE PERIOD (MONTHS)	AVERAGE TOTAL CUTANEOUS DOSAGE (r)
Seminoma	12.1	11,695+
Seminoma and embryonal carcinoma	13.0	16,811
Seminoma and teratoma	2.0	13,000
Embryonal carcinoma	4.0	11,345+
Teratocarcinoma	5.7	12,329+
Teratocarcinoma and chorio-epithelioma	2.0	10,664
Reticulum cell sarcoma	3.0	4,840
Leiomyosarcoma	3.0	7,140
Lymphosarcoma	24.0	12,200
Average (exclusive of sarcoma)	6.5	12,320

At the time of operation 13 patients had blood vessel or lymphatic extension up the cord; thus, nearly a third of these testes demonstated presumptive evidence of metastases or definite extension. The interval between onset of symptoms and definitive therapy in these 13 cases was approximately one year. In most instances the patient was responsible for the delay; in others the physician had procrastinated. The necessity for careful examination, prompt diagnosis, and rapid execution of treatment in suspicious cases, therefore, cannot be overstressed.

The average inclusive period of radiation therapy, exclusive of sarcoma, was about six and a half months. The total average cutaneous dosage, again exclusive of sarcoma, was approximately 12,000 r. (table 16).

RESULTS

It is possible to evaluate five or ten-year survivals in only a portion of the series, since insufficient time has elapsed in some patients. Complete data will not be available until the end of 1955 when the five-year interval will have elapsed for the last patients in the series.

At the time of preparing this report (April 1953), 48 of the 80 patients were living and 29 had died—a mortality of 36 per cent; 3 patients were definitely lost to follow-up.

Table 17 presents the average survival time of the 48 living patients, classified as to the type of tumor. The average interval since operation is 47.8 months. The longest survivals are in the seminoma group, with 3 ten-year survivals and 9 five-year. The embryonal carcinoma and teratocarcinoma groups each have 2 five-year survivals to their credit.

In table 18 are presented survival periods of the 29 patients who have died. Here again those with seminoma survived longer periods, the longest being 44 months and the average 15 months.

Of significance is the fact that in the living patients the lapse between onset of symptoms and surgical intervention averaged 6 months whereas this period in the group who have died averaged nearly eleven months—a contrast that again points to the urgent need for early diagnosis and prompt treatment.

TABLE 17. *Intervals since operation in patients who are living*

	NUMBER PATIENTS	AVERAGE SURVIVAL
Seminoma	28	7 years, 4 months
Embryonal carcinoma	11	3 years, 5 months
Embryonal carcinoma and Chorioepithelioma	1	2 years, 6 months
Teratocarcinoma	7	3 years, 8 months
Leiomyosarcoma	1	3 years
	48	3 years, 11.8 months

TABLE 18. *Postoperative survival of patients who have died*

	NUMBER PATIENTS	AVERAGE SURVIVAL
Seminoma	6	1 year, 9 months
Embryonal carcinoma	10	11 months
Embryonal carcinoma and Chorioepithelioma	2	8 months
Teratocarcinoma	7	1 year, 1 month
Teratocarcinoma and Chorioepithelioma	1	1 year, 2 months
Reticulum cell sarcoma	2	10 months
Lymphosarcoma	1	2 years
	29	1 year, 3 months

TABLE 19. *Metastases recorded at 19 postmortem examinations*

	NUMBER PATIENTS	NUMBER ORGANS INVOLVED
Seminoma	5	29
Embryonal carcinoma	5	17
Embryonal carcinoma and Chorioepithelioma	3	19
Teratocarcinoma	3	11
Teratocarcinoma and Chorioepithelioma	2	8
Lymphosarcoma	1	7

In 19 of the 29 fatalities postmortem examination was done (table 19). The regional nodes were involved unilaterally in 2 cases and bilaterally in 15. Other organs involved, in order of frequency, were liver, lungs, vertebrae, pancreas, kidney, adrenals, cerebrum and stomach.

It was considered, heretofore, that seminomas metastasize late and that metastases occur in lymph nodes predominantly and in other organs rarely. In this series, however, although in only 5 of the 19 autopsies was a seminoma the primary tumor, the average number of organs involved in metastatic spread from seminoma was greater than was determined in the other testicular tumors. Curiously, seminomatous metastates to the cerebrum or cerebellum were not found, despite the widespread involvement of other anatomic sites. In all other types of teratoid tumors numerous metastases were noted in the contents of the

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BILATERAL CONCOMITANT SEMINOMA

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Concomitant malignant testicular tumors in normally placed testicles are rare. There is not a case in the Tumor Registry of the Army Institute of Pathology at Washington, D. C. Hamilton and Gilbert[1] analyzed 7,000 case records of testicular tumors and found 134 cases in which each testicle was involved in cancer at some time. These cases were not of simultaneous involvement and frequently months and years elapsed between involvement of the remaining testicle after removal of the other, thus not ruling out metastasis. In 1949, Hotchkiss and Laury[2] in reviewing the medical literature to the year 1805 were able to find only 21 cases and reported one of their own. Since this review one additional case[3] has been added which, with the case to be reported, brings the total number of cases to twenty-four. If an analysis of the cases of concomitant involvement of the testicles by malignant tumor is further studied it is found that of the 23 cases reported only twelve fall into the classification of primary testicular malignancy as described by Moore or interstitial cell tumor with the remaining cases being of lymphoid or sarcomatous origin. Of the twelve patients with primary testicular tumors six are of embryonal carcinoma,[4, 5, 6, 7, 8, 9] two of encephaloid tumor,[10, 11] type indiscernible, two of interstitial cell tumor,[3, 12] one of carcinomatous teratoma,[13] and one of adenocarcinoma.[14] The case to be reported brings the total number of bilateral primary testicular tumors in normally placed testicles to thirteen.

This is the first case of bilateral seminoma arising concomitantly in normally placed testicles. The patient is living 32 months following treatment with no evidence of disease, which is unusual. He maintains normal libido in the absence of both testicles. Emphasis should be placed on earlier diagnosis of testicular malignancy by considering any mass adjacent to the testicles malignant until proved otherwise. In this case five physicians examined the patient and not one suspected malignancy.

CASE REPORT

J. C. D., a 40 year old white male railroad conductor, was admitted to the Medical College of Virginia Hospital on July 17, 1950, with a chief complaint of

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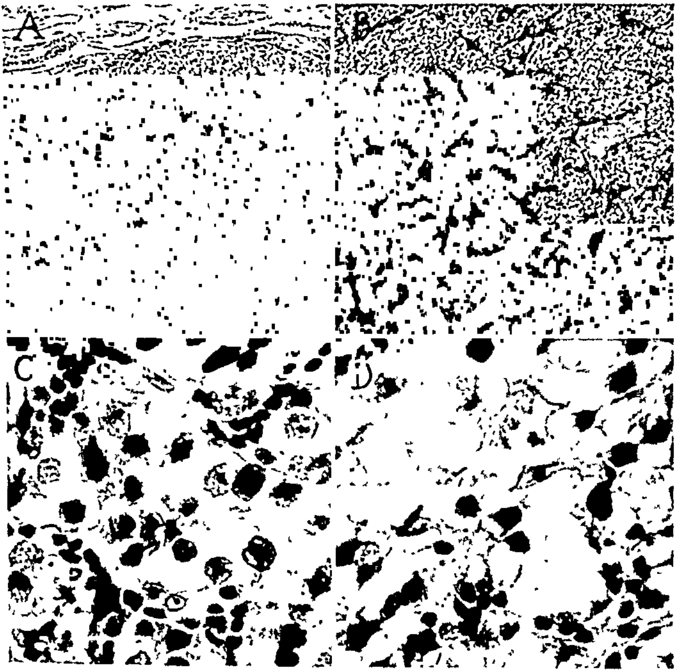

FIG. 1

"swollen testicles" for 6 months. Six months prior to admission the patient was seen by a local physician for swelling of the left testicle and at this time swelling at the base of both testicles was detected with hardness and induration. He gave no history of gonorrhea, stricture, or prostatism and had no urinary symptoms. The patient had had no chills and no fever with no weight loss, and there was nothing in the history to suggest tuberculosis. The patient was given penicillin therapy and sitz baths periodically with no improvement, and because the testicular swelling increased with more hardening but little pain he was admitted to this hospital.

Laboratory examinations revealed nonprotein nitrogen 28, hemoglobin 14, with 4,800,000 red blood cells and a white count of 7,300 with a normal differential. The urine was normal, the Wassermann test negative, and a chest film was within normal limits.

Physical examination revealed a well-developed, well-nourished man lying comfortably in bed not appearing acutely nor chronically ill. The temperature was 98.4, pulse 82, respirations 20, and blood pressure 120/80. The positive physical findings were limited to the genitalia. Both testicles felt normal except in the region of the power pole, which was poorly defined and could not be distinguished from the head of the epididymis which was felt to be thickened on both sides. Both vasa felt normal. The preoperative diagnosis was bilateral chronic epididymitis and the patient scheduled for bilateral epididymectomy.

The testicles were exposed through curved incisions beginning on either side at the external ring and extending down into the scrotum. The testicles revealed a whitish, rounded, firm lesion at either lower pole with fibrosis of the adjacent epididymis. Neither testicle was grossly enlarged. A frozen section was done on each testicle and the diagnosis was seminoma. Following this, bilateral orchiectomy was carried out by ligating each spermatic cord and adjacent structures in turn high in the inguinal canal. The wounds were closed in layers.

Pathological report: Grossly the right testicle measured 4 by 4 by 1½ cm. and the left 3½ by 3½ by 1½ cm. Both testicles at the lower pole adjacent to the epididymis showed a grayish white tumor measuring 1 by 1 by 1½ cm. and displacing the testicular tissue. The epididymides showed some thickening bilaterally.

Microscopic and histological appearance revealed an identical picture in sections of the right and left testes (fig. 1, *A* and *B*). This comprised a tumor made up of polyhydral and rounded cells of uniform arrangement (fig. 1, *C* and *D*). Formations of alveolar configurations separated by collagenous stroma were seen. No acini were evident. There was slight variability in the size of the cells. For the most part, the cell borders were distinct and delineated abundant cytoplasm with clear or faintly granular cytoplasm. In some of the tumor cells the cytoplasm had a reticular appearance. The nuclei were distinctive, being uniform, round or oval, and centrally placed. Tumor giant cell formations were rarely seen. In the typical neoplastic cell the nuclear chromatin filaments or granules were evenly dispersed and varied somewhat in amount from one cell to the other. The majority of the cells contained one prominent nucleolus but two or three such structures were frequent. Pathological or heterotype mitoses were abundant. Practically all of the cells were hyperchromatic.

The stroma in section from both testes was abundant, consisting of dense bands of collagen and reticulum embedded in which were numerous lymphocytes or lymphoid cells. Occasionally lymphoid follicles with germinal centers were obvious. Plasma cells and eosinophilic granulocytes also contributed to the stromal cellular content.

No multinucleated giant cells of the foreign body types were seen. "Epithelioid" cells were absent. The vascularity appeared to be confined to the capillaries running in the connective tissue stromal bands.

The seminiferous tubules adjacent to the tumor mass showed some atrophy. At a distance, however, they were preserved and revealed active spermatogenesis. Atrophic tubules were seen here and there within the tumor. The epididymides appeared free of involvement. Diagnosis: Seminoma of the testes, bilateral (Gordon R. Hennigar, M.D.).

Postoperatively the patient received an average of 2000 roentgens to the lumbosacral area, the aortic nodes, and the mediastinum up to and including cervical seven. This was delivered through multiple ports 10 by 20 cm. in size at a 50 cm. distance using 200 K.V., 20 milliamperes and ½ cm. of copper over a period of 20 days. When last heard from, 32 months following completion of treatment, the patient was living and well with no evidence of tumor and maintaining normal libido.

SUMMARY

The first recorded case of bilateral seminoma is presented which occurred concomitantly in both testicles. Following bilateral orchiectomy and x-ray therapy the patient is living and well 32 months with no evidence of disease and no impairment in potency. The importance of considering all masses in the scrotum, particularly those adjacent to the testicle, as malignant until proved otherwise is emphasized.

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THE USE OF SOLUSPONGE IN PROSTATIC SURGERY

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Even with the advances in the development of new absorbable hemostatic materials the control of bleeding after removal of the prostate is not always wholly successful.

"Solusponge is a physical modification of pure starch, possessing exceptionally high and innate hemostatic properties. These properties are due to the innumerable cell-like spaces which expose a great surface area to the shed blood, and also to the breakdown of sugar products which are released in high concentration on its surface. Such concentrated sugar solutions cause agglutination of red corpuscles and facilitate the clotting action".[1]

The use of Solusponge in Urology was first described by Ritter who carefully studied both the hemostatic and absorptive properties.[2]

The methods of using it and its effect on postoperative care will be discussed. Solusponge comes unsterilized in rectangular strips measuring 2 by 2 by 8 mm. and in two sizes of cones which can be sterilized by autoclaving. Any of the antibiotics or liquid hemostats can be used to impregnate the starch before use.

Our best results were obtained by using one of the following methods. After the prostate has been removed and the arterial bleeding controlled and the prostatic capsule contracted, then the rectangular strips are packed so as to completely fill the prostatic bed. These dry strips are placed in the bed and firmly held in place for one minute with pressure. If a Foley catheter is used the strips are used in a similar manner with one strip on each side around the catheter. The balloon is then blown up and pulled down compressing the sponges in the prostatic cavity. It is held in place by traction on the catheter to the leg for 3 to 4 hours.

A careful study of 75 cases in which Solusponge was used shows in general very few differences as compared with other hemostatic agents.

Two cases had mild secondary hemorrhages controlled by transfusions. The sponge had apparently been ejected into the bladder when the pressure had been relieved.

Two other cases passed small gelatinous pieces of tissue for 8 to 13 days after operation. They were washed out of the bladder by irrigation through a catheter but in no instances were calculi found or was operation for removal necessary. Analysis of these tissues showed no evidence of starch granules and to date no cause has been found for their production.

A comparison with other methods of controlling bleeding shows equally good hemostasis and there is no difference in the number of type of spasms occurring in convalescence. Wound closure is not hastened. Severe postoperative hemorrhage has not occurred in this series.

In summary, Solusponge is a useful hemostatic agent in prostatic surgery. It is easy to handle and is an effective agent in control of bleeding. Its suitability for impregnation with antibiotics may be of value.

180 Fort Washington Ave., New York 32, N. Y.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Hot Springs, Va. May 6-8, 1953.

[1] Pamphlet describing Solusponge.

[2] Ritter, J. S., and Bloomberg, H.: Solusponge as a hemostatic agent in Urology. J. Urol. 67: 543-546, 1952.

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RETROPUBIC PROSTATECTOMY WITH DIVERTICULECTOMY AS A ONE STAGE PROCEDURE

H. VERRILL FINDLAY AND P. PAUL RIPARETTI

Diverticulum of the bladder is a reasonably common urological lesion, but has been discussed very little in the recent literature. Senger reported 88 diverticula in 12,000 urological patients, or a ratio of one for every 136 admissions to his clinic. There were thirteen males for every female. Burns states that "diverticulum of the urinary bladder is a complication of clinical importance in about 6 per cent of cases of obstruction at the bladder neck." Because we have combined the operations of diverticulectomy and retropubic prostatectomy as a single procedure, we believe a presentation of our experience is justified.

A diverticulum is a herniation of the bladder mucosa through the muscular wall of the bladder producing a sac which is lined with mucosa and covered with few or no strands of muscle. The usual site of the orifice is in the base of the bladder close to one of the ureteral openings. At this point the bladder musculature is supposedly weakened by the insertion of muscular fibres of the ureteral wall into those of the bladder. Most diverticula are associated with some type of bladder neck obstruction and occur chiefly in males of the prostatic age.

The condition was first reported in 1700 by Bartholin, who found at autopsy a diverticulum of the bladder in a huge scrotal hernia. Morgagni, in 1730 postulated that diverticula of the bladder were caused by bladder neck obstruction which he presumed to be due to enlargement of the prostate.

In 1895 Pean performed the first successful diverticulectomy, and in 1919 Hinman collected 205 cases from the literature, adding 20 of his own. Judd and Scholl, in 1924, reported 87 surgical cases from the Mayo Clinic, with a 7 per cent mortality. They advised the two-stage procedure, doing the diverticulectomy first and establishing bladder drainage, followed by the prostatectomy as a secondary procedure. In 1928 Lowsley and Guiterrez reported some 39 cases, 40 per cent of which were not subjected to operation. The symptoms were usually those of urinary infection associated with bladder neck obstruction. Dees described 95 cases from the Johns Hopkins Hospital in 1940, of whom 78 had demonstrable bladder neck obstruction. He used preliminary suprapubic drainage, even for as long as 40 days. The mortality from diverticulectomy was 10 per cent. The same year Thompson reported 96 patients with the condition from the Mayo Clinic, on whom he had done transurethral resection without attacking the diverticulum. Eighty-eight of them had small prostates, an average of 18 grams of tissue being removed.

Barnes, in 1939, gave his experience with marsupialization of a diverticulum which was so adherent that it could not safely be entirely removed. The technique has been reported more recently by others who have used various cauterizing agents to destroy the mucosal lining of the sac.

Couvelaire, in 1948, reported having done a diverticulectomy and a retropubic prostatectomy as a combined procedure. From a 66 year old man with 420 cc of

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Read at annual meeting, Western Section of American Urological Association, San Francisco, April 27–30, 1953.

residual urine he removed a prostate weighing 62 gm. The patient made an uneventful recovery with, however, 19 days of postoperative hospitalization.

Diverticulum of the bladder may be suspected in any patient who has a large residual urine, especially a man in the "prostatic age group." The typical patient will have the symptoms of prostatism, usually with an infected residual urine. Occasionally on physical examination the bladder or diverticulum may be sufficiently distended to be palpable suprapubically. The prostate may be a large adenoma, but is frequently of the small fibrous type. Pyuria or hematuria may be found, and bladder stones or tumor may be associated. The diagnosis is made from the history and physical findings, cystoscopy, and cystogram.

Treatment is dictated largely by the severity of the symptoms and findings. Many patients with only a small diverticulum, a minimal residual urine, and mild symptoms may best be treated conservatively by controlling their urinary infection. With a small type of fibrous obstructing prostate and a relatively small diverticulum, a transurethral resection of the gland will relieve the obstruction and allow the diverticulum to drain adequately so that the infection can be easily controlled. If the sac remains large a diverticulectomy is required. In the individual with a large diverticulum, a chronically infected residual urine, and a large prostate, some type of open operation is usually necessary to secure real relief. Often in the past these patients have required prolonged suprapubic drainage to control their infection and make them satisfactory surgical risks. As a rule the diverticulectomy was done at the time the drainage was instituted and the prostatectomy left for the second session.

Diverticulectomy and retropubic prostatectomy as a combined procedure has been recently done by us on three patients without mortality. The results have been most satisfactory and the duration of hospitalization, with its attendant expense, has been materially shortened.

The surgical technique is not particularly complicated, with some variations to meet the individual problem. The patient is placed in a modified Trendelenburg position and the bladder filled sufficiently to distend the diverticulum. The amount of fluid necessary is estimated from the previous study of the residual urine and from the cystogram. A midline suprapubic incision is made, and the bladder and diverticulum exposed. With the diverticulum still distended its dissection from the surrounding tissue is relatively easy until one reaches the region of the neck, which may be deep in the pelvis. At this point it may be necessary to empty the bladder in order to have space in the pelvis to work. Traction is then applied to the diverticulum and the neck and attachment to the bladder are dissected free and exposed. The diverticulum is excised close to the bladder orifice and the bladder mucosa is examined through this opening. A layer of 00 chromic catgut is used to invert the bladder mucosa, and a second layer of 0 chromic to close the muscular defect at the orifice. Hemorrhage is usually very slight if most of the dissection is done with the finger in separating the diverticulum from the surrounding tissue. This procedure is entirely extravesical.

The diverticulum having been removed and the bladder closed, the retropubic prostatectomy is done by the technique described by Millin, Bacon, and others.

We are careful to remove an adequate wedge of tissue from the floor of the bladder neck. After bleeding is controlled a 24F Foley catheter is inserted through the urethra into the bladder and distended with 60 cc of fluid. The incision in the prostatic capsule is then closed with interrupted sutures of No. 0 chromic. The catheter is irrigated to be sure that it is not obstructed and draining freely. Cigarette drains are placed to the region of the neck of the diverticulum and to the retropubic space. The rectus sheath and the skin are closed separately. At least one transfusion is given during the procedure.

Postoperatively all the patients have done well. They are given adequate fluids, sedation, and antibiotics. We are inclined to leave the catheter in place for as long as 12 days. The suprapubic drains are removed on the fourth day if there is no evidence of leakage or infection. On removal of the Foley catheter all the patients have voided freely with good control and no residual urine of consequence. Follow-up cystograms have shown uniformly satisfactory results.

CASE REPORTS

Case 1. A 64 year old man was first seen on June 22, 1951 complaining of hesitancy, straining, small stream, and nocturia, which had been present for over a year. He was a small thin man, and did not appear acutely ill nor uncomfortable. The prostate was graded 2 plus, elastic and adenomatous in texture. He voided slowly and was found to have 350 cc of clear residual urine. Urological study was recommended. He did not return until 6 weeks later when he had a rather severe hematuria of several hours duration. He now had an apparently distended bladder from which a large amount of urine and clots were evacuated. He was sent to the hospital with a Foley catheter in place.

Urograms revealed a normal upper urinary tract, but the cystogram showed two large bladder diverticula which looked like the ears of a caricature in the Sunday comics. Cystoscopy showed coarse bladder trabeculation, moderate intraurethral intrusion of the lateral lobes of the prostate, and a diverticulum opening just lateral to each ureteral orifice. Blood studies were normal, and his internist felt that he was an excellent operative risk.

The operation was done on August 8, 1951. The procedure as outlined was followed except that both diverticula were dissected free before either was opened. The prostatectomy was somewhat difficult because the gland was relatively small and rather adherent. His convalescence was uneventful and he was discharged from the hospital on the fourteenth postoperative day. The pathologist reported nodular hyperplasia of the prostate weighing 24 gm.

Cystograms made on January 2, 1952, some 5 months later, showed that he had no defect in the bladder and excellent emptying. The urine was clear.

Case 2. A 67 year old white man came into the office with a Foley retention catheter in place. He had suffered a complete urinary retention three days before, and "three quarts of urine" had been removed elsewhere. He was an alert intelligent man, and appeared to be quite comfortable. He said that several months previously he had been on a long automobile ride and had retained the urine until he was quite uncomfortable. At this point the car went over a sudden hard bump and he had a very severe pain in his pelvis, followed by relief from his intense desire to void. However, following this episode he had no increase in the symptoms of prostatism from which he had suffered for several years. For a week prior to the present retention the symptoms had been increased and he had been voiding more frequently than usual. There had been no hematuria nor pyuria, and this was his first experience with urinary retention.

Rectal examination showed an enlarged adenomatous prostate which was graded 3 plus. Excretory urograms revealed a medial deviation of the lower right ureter as though it were displaced by some mass in the pelvis. Cystograms showed a large diverticulum on the right side which was obviously pushing the ureter out of its normal alignment. Cystoscopy was done and marked trabeculation of the bladder and a big trilobar hypertrophy of the prostate were found. Near the right ureteral orifice there was the opening of a large diverticulum. The blood count and chemistry were normal, and his physician felt that his general condition was good except for slight myocardial damage.

The combined operation was done a few days later. It was not particularly difficult, though he was a rather obese man. When the lowermost portion of the diverticulum was being dissected the ureter was seen and carefully freed without any damage. The mouth of the diverticulum was closed. The retropubic prostatectomy was easily done, though there was rather more bleeding than usual. He left the hospital on the eleventh postoperative day, voiding a good stream and with excellent control. The pathological report was benign adenomatous hypertrophy of the prostate, and the specimen weighed 61 gm.

Six months later this patient's cystogram showed no diverticulum and there was no residual urine. The urine was grossly clear and the result considered most satisfactory.

Case 3. A 64 year old man was first seen in the hospital some 13 days after the surgical repair of a left inguinal hernia. After his operation he had developed an acute urinary retention and was wearing a Foley catheter. He also had a subsiding left epididymitis which increased his disability. He admitted symptoms of prostatism for the last 3 years,but no previous urinary retention. Rectal examination revealed a rather broad flat adenomatous prostate, graded about 3 plus.

Cystoscopy a week later demonstrated a considerable degree of coarse trabeculation of the bladder, a trilobar intravesical intrusion of the prostate, and the mouth of a diverticulum lateral to the left ureteral orifice. Excretory urograms showed a normal upper urinary tract and the cystogram outlined a large diverticulum on the left side of the bladder. His blood findings and blood chemistry were normal.

The operation was performed a few days later. The diverticulum was easily separated and the opening closed easily. The retropubic prostatectomy presented no unusual problem. His postoperative course was a little prolonged on account of his preceding troubles and also because he was a bachelor living in another city. He remained 30 days in the hospital on this account, though his surgical condition would have permitted his discharge on the sixteenth day. The pathologist reported a benign adenomatous prostate weighing 50 gm.

Follow-up cystogram was made 5 months after the operation and revealed no diverticulum and no residual urine. Since he had a good stream and excellent control we considered the result entirely satisfactory.

SUMMARY

Diverticulum of the bladder must be suspected in any patient with a large residual urine and with symptoms of bladder neck obstruction. If suspected, the diagnosis is easy and definite. Treatment may be nonoperative if the sac is small, the residual slight, the urine clear, and there are no obstructive symptoms. Transurethral resection will relieve many patients with small prostates and small diverticula. Patients with large glands and large sacs are best treated by diverticulectomy and open prostatectomy.

We present our experience with 3 patients upon whom we have combined diverticulectomy and retropubic prostatectomy as a one-stage procedure. There was no mortality, the hospital expense was reduced by the shortened convalescence, and the postoperative results have been most gratifying.

Santa Barbara, Calif.

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RETROPUBIC PROSTATECTOMY: A REVIEW OF 678 PATIENTS

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This is a survey of 678 patients having undergone retropubic prostatectomy during the 6-year period from 1947 to 1953. The discussion will neither set forth the method nor extol the merits of this procedure. However, to provide a more comprehensive perspective of the status of retropubic prostatectomy I have included a comparable number of cases from both the domestic and foreign literature.

In this group of 678 retropubic prostatectomies there is included 171 patients operated upon by the resident staff of the Louisville General Hospital. All other patients were private patients upon whom the surgery was performed by the late Dr. Owsley Grant, Dr. Joseph E. Maurer and the author.

This series of retropubic prostatectomies includes a 22 month period during which other types of prostatectomy were seldom done. Actually this program was stimulated by correspondence between Dr. Owsley Grant and Mr. Terence Millin. Dr. Grant was anxious to substantiate our contention of perineal superiority and at the same time demonstrate the limitations of Mr. Millin's procedure. Following this initial series of retropubic prostatectomies we resumed our previous practice of employing open prostatectomy only in medium to large prostatic adenoma (in excess of an estimated 60 gm.) (fig. 1).

The following topics have been chosen as the basis for our evaluation of retropubic prostatectomy:

1) Postoperative hospital stay (days)

2) Complications: a. Osteitis pubis; b. secondary hemorrhage; c. mortality. There are of course many additional subjects that might be discussed: Vesical neck contractures, necessity of transfusion due to blood loss at the time of surgery, length of catheter period, etc. all are of interest, but the significance of these complications would certainly be reflected indirectly by the topics chosen for comparison. May I say at this point that we have experienced three vesical neck contractures in our series and all in the first 50 patients when we did not understand when and how much of the vesical neck need be resected. In our private patient series the number of transfusions has been less than 12 per cent while in the general hospital series it approaches 90 per cent. This variation is due to our conservative attitude; whereas, in the general hospital the condition of the patients is less good and the popularity of transfusion is evident on all services.

The domestic and foreign series of retropublic prostatectomies for comparison were chosen at random from the literature based only on obtaining a total group size comparable to our series.

In reviewing tables 1, 2 and 3 there is apparent a remarkable similarity (fig. 2). The increased period of postoperative hospitalization in the foreign series is probably not significant since the time of the retention catheter and postoperative complications did not account for a prolonged hospital stay. It would seem that some other factor must be responsible that was not presented.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Hot Springs, Va. May 6–8, 1953.

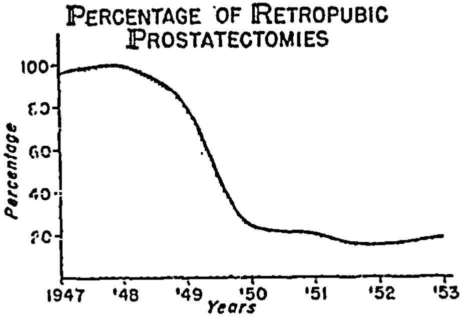

FIG. 1. Percentage of retropubic prostatectomies done annually 1947–1953

TABLE 1. *Domestic series of retropubic prostatectomy*

AUTHORS	NUMBER CASES	POSTOPERATIVE HOSPITAL DAYS	PERCENTAGE OSTEITIS PUBIS	PERCENTAGE SECONDARY HEMORRHAGE	PERCENTAGE MORTALITY
Hand and Sullivan	100	13.5	0.0	0.0	0.0
Bacon	102	12.6	0.9	0.9	6.8
Toulson, Mays and Hawkins	105	14.3	0.0	0.0	4.7
Moore	116	10.6	11.2	0.0	1.7
Slotkin	119	11.6	0.0		1.6
Scheinman	121	11.4	0.0	0.0	0.0
Total	663	Average...12.3	2.0	0.9	2.4

TABLE 2. *Foreign series of retropubic prostatectomy*

AUTHORS	NUMBER CASES	POSTOPERATIVE HOSPITAL DAYS	PERCENTAGE OSTEITIS DAYS	PERCENTAGE SECONDARY HEMORRHAGE	PERCENTAGE MORTALITY
Ostenfeld	114	23	4.3	6.1	5.0
Hickey	50		2.0		2.0
Jacobs	500	16	0.6	0.2	6.0
Total	664	Average...19.5	2.4	3.1	4.3

Osteitis pubis is unquestionably the most disquieting factor in retropubic prostatectomy. It is disturbing because of the variable incidence reported (ranging from 0 to 17 per cent). In discussing this complication with authors who have found it most troublesome, we find no apparent difference in technique and often the author reporting the greatest difficulty seemingly exerts great effort in its prevention. Antibiotics are not a factor for we have done many in which neither antibiotics nor any of the sulfonamides were used. Infections in the space of Retzius are not necessarily significant and we have not found any correlation (fig. 3).

TABLE 3. *Present reported series of retropubic prostatectomies*

AUTHORS	NUMBER CASES	POSTOPERATIVE HOSPITAL DAYS	PERCENTAGE OSTEITIS PUBIS	PERCENTAGE SECONDARY HEMORRHAGE	PERCENTAGE MORTALITY
Total........................	678	Average...12.1	0.7	1.3	1.6

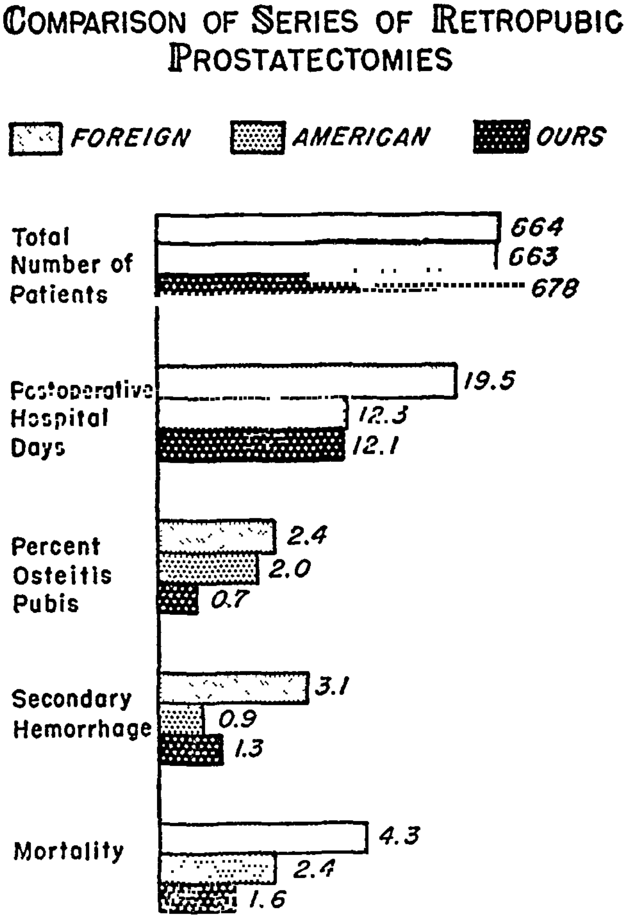

FIG. 2. Comparison of reported series with comparable group of American and foreign authors.

In fact, in only one of our 5 patients with osteitis pubis was there any appreciable visible wound infection. Our incidence of wound infection, of sufficient intensity to warrant additional hospitalization, was found to be 5.3 per cent or a total of 36 wounds. The incidence of osteitis pubis was 0.7 per cent or a total of 5 patients. One of the 5 patients with osteitis pubis occurred in the General Hospital series of 171 patients. Only two patients suffered severe and prolonged symptoms. Millin in reporting 1100 cases of retropublic prostatectomy mentions 9 instances of osteitis pubis; an incidence of 0.8 per cent.

We have used secondary hemorrhage to connote postoperative hemorrhage that has occurred after the initial operative bleeding has subsided. In reviewing

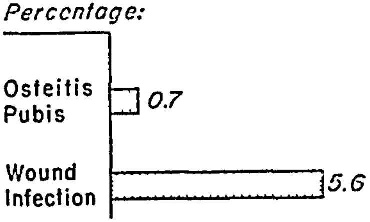

FIG. 3. Relationship between osteitis pubis and retropubic wound infection

the literature it is difficult to judge the definition of secondary hemorrhage as used by some authors. For example, secondary hemorrhage occurring after the catheter has been removed and controlled by re-insertion of a catheter has not been considered in our series to be significant provided that it did not prolong the patient's postoperative course. The criterion used in our series was hemorrhage that necessitated some type of operative intervention. In the group reported it was controlled in all but two of the 9 patients suffering this complication by transurethral fulguration of the bleeding vessel. In two instances the bleeding point could not be localized transurethrally and the operative wound was reopened and the prostatic bed packed which controlled the bleeding immediately. In one instance the bleeding was coming from a large vein in the cut edge of the prostatic capsule anteriorly and in all other patients the bleeding was due to a prostatic artery. Because of these experiences all vessels in the capsular wound edge are securely ligated with a figure of eight suture as are the prostatic arteries. This single variation from Mr. Millin's original technique has put an end to our problem of secondary hemorrhage. We employ fulguration for small oozing points, but never for active arterial bleeding.

In this group of 678 patients there were 11 deaths or an incidence of 1.6 per cent. Except one, all deaths occurred within 14 days following surgery. The one exception was a patient of 73 years who died suddenly 27 days following surgery after he had ridden home, a distance of 58 miles, on his eighth postoperative day. One patient, 56 years of age, died on the fifth day after surgery with an acute coronary thrombosis; another, 78 years of age, had an uncontrollable cardiac decompensation and bronchopneumonia and died in cardiac failure on the thir-

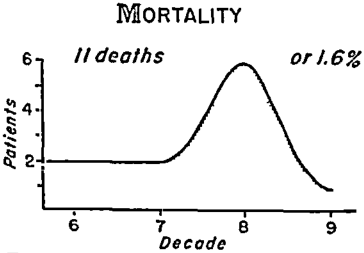

FIG. 4. Comparison of mortality to patient's age

TABLE 3. *Present reported series of retropubic prostatectomies*

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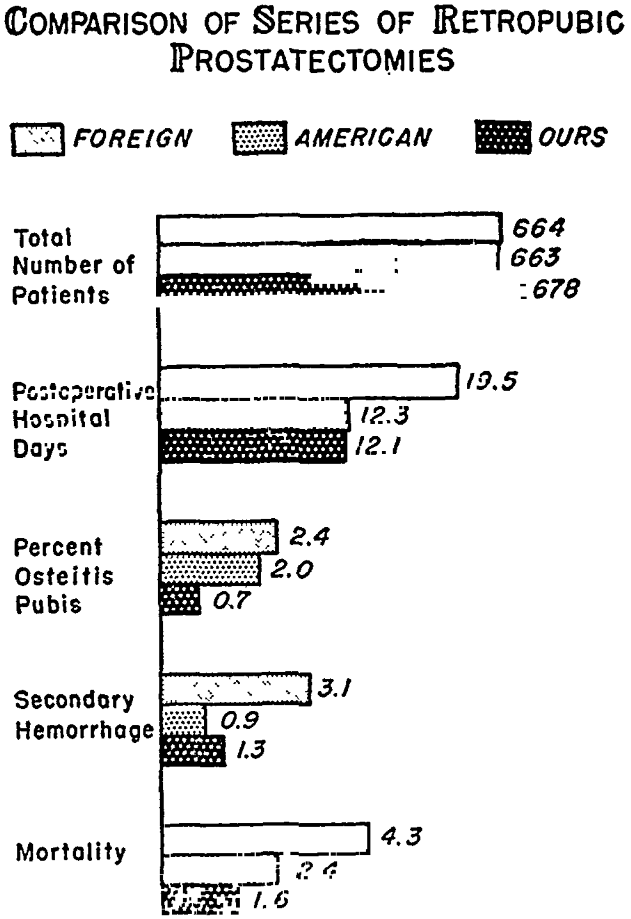

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We have used secondary hemorrhage to connote postoperative hemorrhage that has occurred after the initial operative bleeding has subsided. In reviewing

TABLE 3 *Operative mortality*

TYPE OF OPERATION	NO	MORTALITY RATE
Transurethral	310	2 5%
One stage S P	196	2 2%
Retropubic	12	0 0%
Perineal	12	0 0%

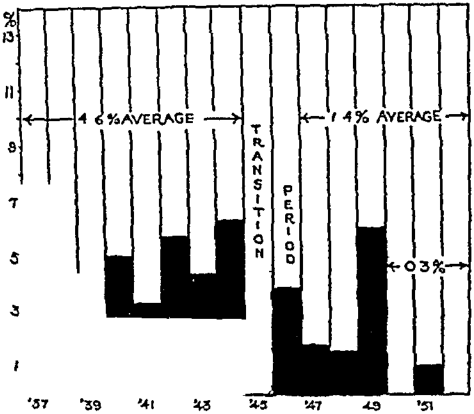

FIG 2 Annual preoperative mortality in public ward patients, Montreal General Hospital

TABLE 4 *Causes of preoperative death*

	1937–1944 8 years	1947 1952 6 years
No of patients	544	539
Pyelonephritis	9	1
Cardiovascular	8	6
P-	3	0
F	2	0
Uremia	0	2
Other causes	2	0
	24	9

Another important change has been the diminution in the incidence of pulmonary embolism In the first group of patients 7 fatal emboli occurred, in the second group only one This further improvement has eliminated an additional 15 per cent of the former deaths The one remaining significant cause of mortality has been disease of the cardiovascular system, but even its incidence has been reduced by half It is not likely that the danger of cerebral hemorrhage or thrombosis or coronary infarction can be removed entirely in this older group of patients

All four, standard, prostatic operations were utilized in the treatment of the more recent group of 530 patients. Most of them, 506 in all, were operated upon by either the transurethral or the one-stage, suprapubic, transvesical procedure. This latter group affords an excellent opportunity for comparing the results of these two operations on the same urological service (table 3). The mortality rate for the two procedures was virtually the same, 2.5 per cent for the one-stage in 196 patients, and 2.2 per cent for the per-urethral in 310 patients. This similarity in mortality rates was somewhat surprising, because an impression had been formed from watching the two groups of patients on the same wards that the mortality in the suprapubic group would be considerably higher. Certainly the suprapubic procedure seems to be a more disturbing operation for the patient, and this fact is borne out by the incidence of immediate postoperative complications, which has been 18 per cent in the one group and 8.3 per cent in the other.

All these changes in operative results are interesting and significant, but the greatest of all seems to be taking place in the reduction of preoperative mortality. In the years 1937 to 1944 there were 24 preoperative deaths with a mortality rate of 4.4 per cent. This is in sharp contrast with the 9 deaths and mortality rate of 1.4 per cent in the period from 1947 to 1952. It would seem that the preoperative fatality rate is still falling for in the past 3 years there has been but a single death, a rate of 0.3 per cent for this three year period. See figure 2.

In the preoperative phase of treatment pyelonephritis again was found to be the commonest cause of death (table 4). It accounted for 9 of the 24 preoperative fatalities in the first group of patients, but was responsible for only 1 in the second group. The incidence of preoperative deaths due to cardiovascular disease in the two groups has remained virtually the same. This may indicate that there has not been a very great change in the general level of health. Deaths from all other preoperative causes have diminished.

The most striking information that has emerged from this study is the startling decrease in deaths due to urinary tract sepsis. It is not likely that this change can be attributed solely to the introduction of antibiotics. Many factors such as less preoperative urethral instrumentation, and greater attention to asepsis have undoubtedly played their part. The change-over from two-stage suprapubic prostatectomy may have had some effect on the mortality rate but under modern conditions the two-stage operation could be performed perhaps with equally good results.

In summary it can be said that the former chief causes of preoperative and operative fatality in prostatic patients virtually have been removed. Further improvement in mortality rates will depend probably on greater attention to the minutiae of treatment and in particular to extreme precautions against cardiovascular accidents.

1414 Drummond St., Montreal, Canada

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IMPORTANCE OF FROZEN SECTIONS IN EVALUATING PROSTATIC NODULES

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It has been axiomatic that precise diagnosis is a prerequisite of rational therapeusis Many ingenious techniques have been devised for histologic study of palpable nodules in the prostate but only perineal exposure of the gland affords direct access to the entire troublesome posterior lamella Biopsy via this route, therefore, should have the greatest potential for indicating unequivocally the bona fide candidates for so called radical operations

The combination of frozen-section examination and simultaneous prostatectomy of appropriate type has no parallel in other diagnostic or therapeutic schemes This theoretically ideal one stage procedure has attained only limited popularity, however, owing to the exacting technical details of perineal dissection or to skepticism regarding the diagnostic value of frozen sections

Our study was undertaken in the hope of answering two pertinent questions 1) Can carcinoma of the prostate, especially early lesions, be diagnosed with consistent accuracy from frozen sections alone and 2) is histologic confirmation of clinical impressions necessarily important when selecting patients for radical prostatectomy?

The survey has been limited to palpable nodules within the prostate of individuals whom we considered suitable candidates for the radical operation This assured inclusion of those lesions which are usually most confusing to pathologists as well as urologists

Each prostate was exposed perineally and a generous sample was taken from the indurated portion In some instances the entire lesion was excised Multiple biopsy specimens were examined when the induration was less impressive after the gland had been exposed and when the first piece of tissue was reported benign

PREPARATION OF FROZEN SECTIONS

The frozen sections were prepared according to a standard technique, as follows The fresh piece of tissue is placed on the stage of a Spencer freezing microtome and frozen with carbon dioxide Sections are cut with an average thickness of 10 to 15 microns One of these is floated on the surface of cold tap water and then transferred on a glass rod to Terry's polychrome methylene blue stain for a few seconds The section is washed in fresh tap water and mounted on a glass slide with a cover slip over it The mounting medium is tap water

Sections prepared in this manner will deteriorate because the fluid evaporates and the stain fades on exposure to light Usefulness of the preparation can be prolonged by sealing the edges of the cover slip with lacquer to prevent evapora-

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Read at annual meeting American Association of Genito Urinary Surgeons, Hot Springs, Va May 6–8, 1953 tion of the water. Most sections, however, can be preserved for only a little more than twenty-four hours.

It is especially important that the sections be fairly thin and well stained, and some experience with the technique of making fresh frozen sections is required. We routinely have residents in pathology and residents from the various surgical specialties cut our fresh frozen sections and find that after one to three weeks of experience, they make reasonably good fresh frozen preparations. A very essential part of the technique is the use of a sharp knife. Our knives are sharpened after a day's use during which they cut 40 to 50 preparations.

INTERPRETATION OF FROZEN SECTIONS

The interpretation of preparations is made by means of low power and high power microscopy.

The carcinomas of the prostate which give the pathologist difficulty in diagnosis are those which produce well-formed acini. When the acinus 1) loses its papillary projection and 2) becomes smaller and when 3) the cytoplasm of the cell takes up fat and is therefore clear, one should suspect carcinomatous changes. It is not sufficient that only two of these criteria be fulfilled. We have found it necessary for all three to be met in order to make a foolproof diagnosis of carcinoma (fig. 1).

Another very helpful feature to look for in fresh frozen sections, as well as fixed sections, is the presence of collars of tumor cells around nerves. Because the piece of tissue under discussion is usually removed from the posterior lamella of the prostate, nerves and vessels are very readily demonstrated.

In order to become expert in the diagnosis of carcinoma of the prostate from fresh frozen sections, one must be familiar not only with the appearance of numerous carcinomas of the prostate in fresh frozen sections but also with the

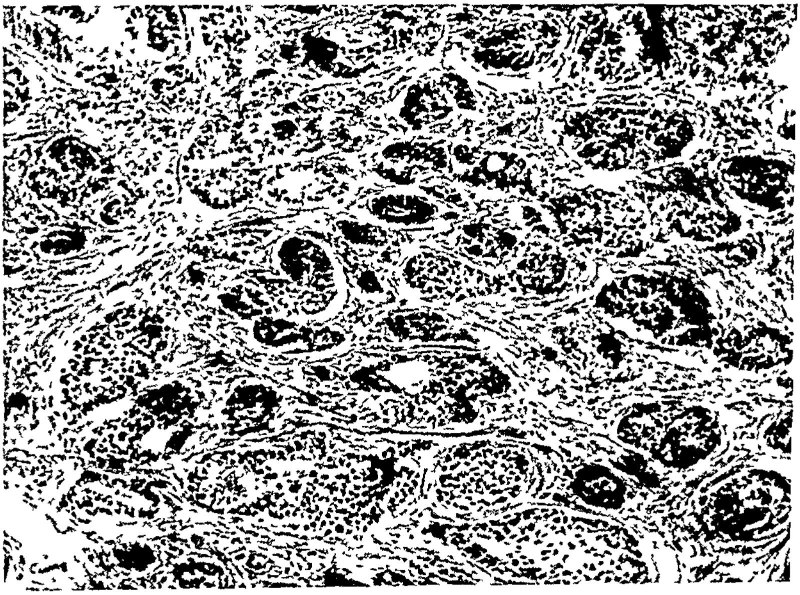

FIG 1. Adenocarcinoma of prostate. Note small lumina, lack of papillary infoldings and cells with clear cytoplasm (fresh frozen section stained with Terry's polychrome methylene blue; ×95).

appearance of benign conditions which mimic carcinoma, such as metaplasia of prostatic epithelium The pathologist who examines questionable lesions of the breast and little else by the fresh frozen technique is probably inadequately prepared to interpret prostatic lesions by this method

ACCURACY OF METHOD

The foregoing morphologic criteria were used to interpret frozen prostatic sections from 45 patients In 40 cases the diagnosis was carcinoma while in 5 instances a benign condition was reported

Each piece of tissue used for frozen section was examined later by means of conventional fixed sections *The original diagnosis was confirmed in every case* Finer details of the permanent sections merely permitted more precise differentiation between grades of malignancy Twelve patients had grade 1 lesions, 26 had grade 2 lesions, and 2 had grade 3 lesions

Admittedly, this is a small series but consistency of this degree has not been unique All our surgical specimens are examined routinely by both frozen and fixed techniques, and the final diagnosis rarely differs from the provisional one

IMPORTANCE OF METHOD

More important than any vindication of the frozen-section technique as a dependable diagnostic procedure is the question of whether or not such studies have significant clinical value, and this we attempted to determine in our study

The 40 patients with positive biopsy specimens were treated by radical perineal prostatectomy All are now impotent, even though 21 are less than 60 years of age, 1 is only 45, and the average age for the entire group is 59 5 years

Four of the 5 patients with benign lesions had no urinary difficulty and the remainder of the prostate was not disturbed The fifth patient underwent simple enucleation of adenomas because of obstructive symptoms The ages of these 5 individuals varied from 41 to 64 years with an average of 55 4 years None has noted any change in his libido or potentia since the operation

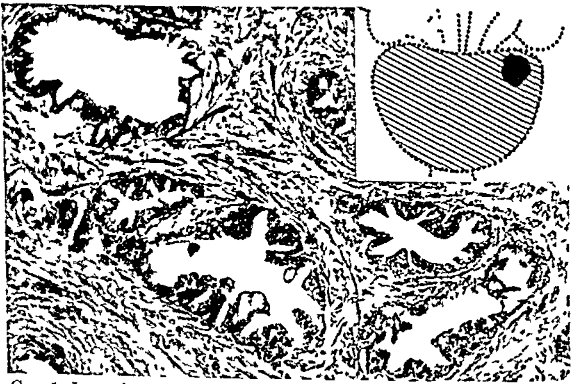

FIG 2 Case 1 *Inset,* diagram of unenlarged prostate showing indurated nodule at base of right lateral lobe Photomicrograph of biopsy specimen taken from nodule shows benign hyperplasia (hematoxylin and eosin, ×65)

It is obvious, therefore, that sacrifice of the entire prostate entails a definite physiologic price which may not be too great for possible "cure" of a potentially lethal disease but one which the unafflicted surgical victim may not accept too philosophically, especially when appropriate preliminary measures could have circumvented this stigma. To date we have found it difficult to be reconciled to prophylactic total prostatectomy.

On the other hand, more serious errors may be perpetrated when patients are denied radical prostatectomy merely because biopsies have not been employed to maximal advantage. Even in retrospect we were unable to discern any special clinical features whereby patients might have been selected for operation more discriminantly. Without adequate biopsies there would have been inevitable errors of omission as well as of commission. Included in our series of 45 cases were several striking examples of potential pitfalls in the simple palpation of prostates.

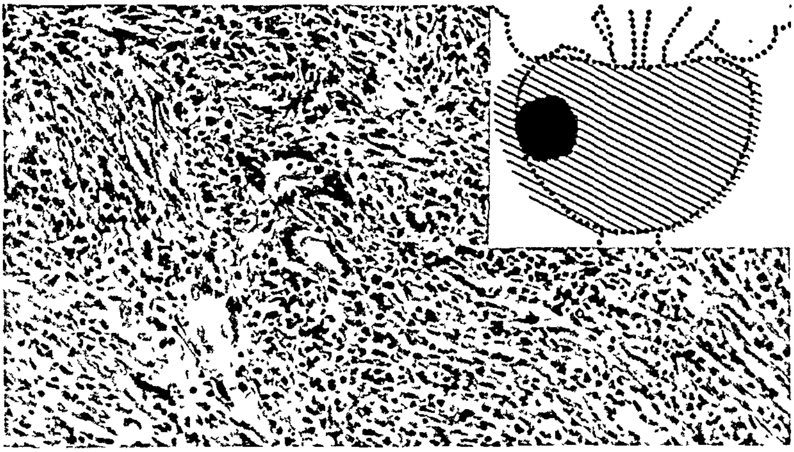

FIG. 3. Case 2. *Inset*, diagram of prostate showing slightly enlarged left lobe which contains a palpable nodule. Photomicrograph of biopsy specimen taken from nodule shows granulomatous prostatitis. Note giant cells (hematoxylin and eosin; ×160).

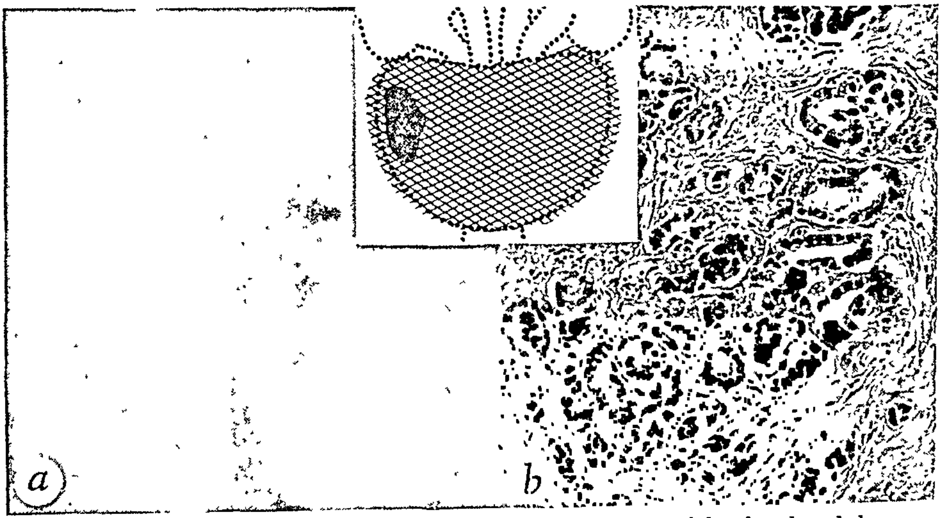

FIG. 4. Case 3. *Inset*, diagram of diffusely indurated prostate with a hard nodule near the left lateral border. *a*, Plain roentgenogram showing multiple prostatic calculi. *b*, Photomicrograph of biopsy specimen taken from nodule showing adenocarcinoma (hematoxylin and eosin; ×135).

ILLUSTRATIVE CASES

Cases 1 and 2, to follow, were thought to be classic examples of early prostatic malignancy.

Case 1. A patient, aged 41 years, had been treated successfully for lymphosarcoma of the neck and had a stony-hard nodule near the base of the right lateral lobe of an otherwise normal prostate. Biopsy showed benign hyperplasia (fig. 2).

Case 2. A patient, aged 57, had an area of third degree induration in the slightly enlarged left lateral lobe of the prostate. Frozen-section examination revealed a localized area of granulomatous prostatitis (fig. 3).

In the other 3 instances of benign disease the condition proved to be either benign hyperplasia or granulomatous prostatitis despite multiple biopsies.

The hazards of hasty interpretation are illustrated by case 3.

Case 3. A 57-year-old patient with diffuse induration in the prostate had been

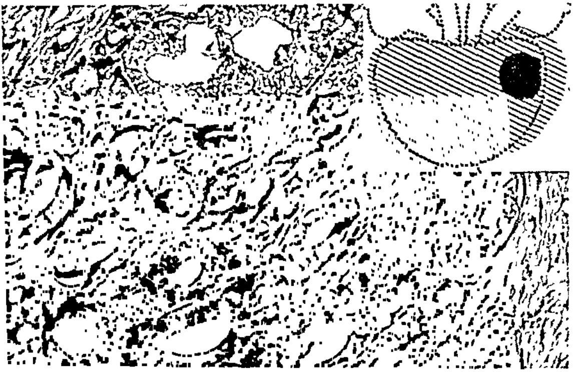

FIG. 5. Case 4. *Inset*, diagram of prostate showing palpable nodule on right. Photomicrograph of biopsy specimen taken from nodule shows adenocarcinoma (hematoxylin and eosin; ×160).

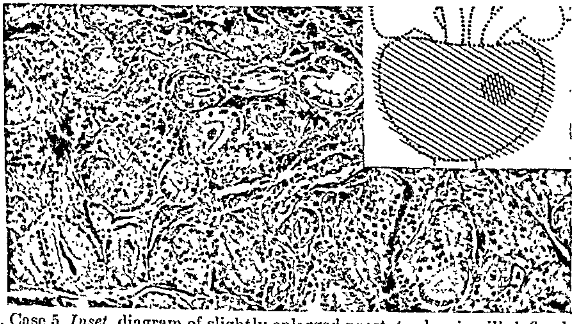

FIG. 6. Case 5. *Inset*, diagram of slightly enlarged prostate showing ill-defined nodule on right side. Photomicrograph of biopsy specimen taken from nodule shows adenocarcinoma (hematoxylin and eosin; ×110).

found to have prostatic calculi, and no treatment had been advised. One area on the left was much firmer than the remainder of the gland. Frozen-section examination disclosed adenocarcinoma (fig. 4).

The importance of continued observation is demonstrated by case 4.

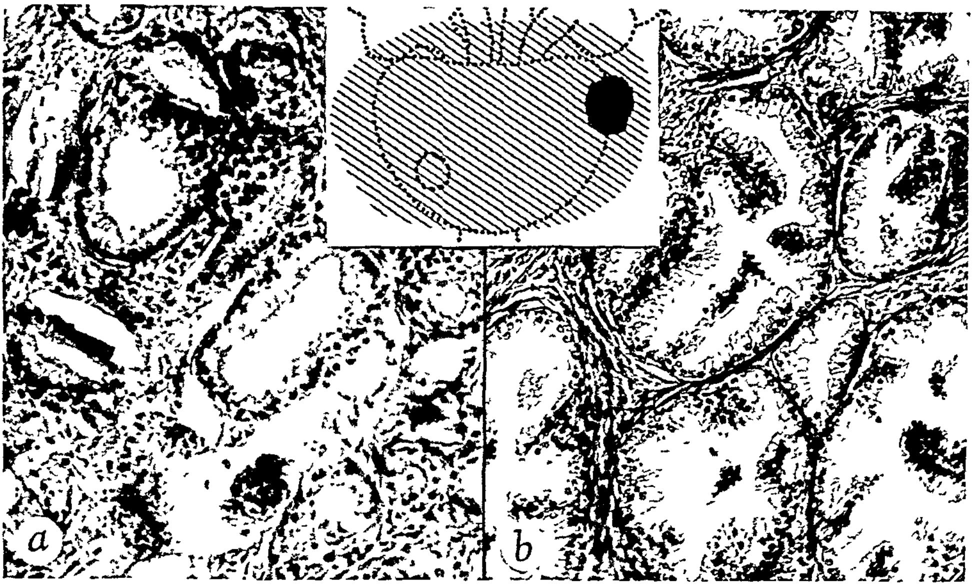

Fig. 7. Case 6. *Inset*, diagram of diffusely enlarged prostate showing markedly indurated nodule on right and site of random biopsy on left. *a*, Photomicrograph of biopsy specimen taken from nonindurated left side showing adenocarcinoma (hematoxylin and eosin; ×150). *b*, Photomicrograph of biopsy specimen taken from indurated portion showing benign hyperplasia (hematoxylin and eosin; ×115).

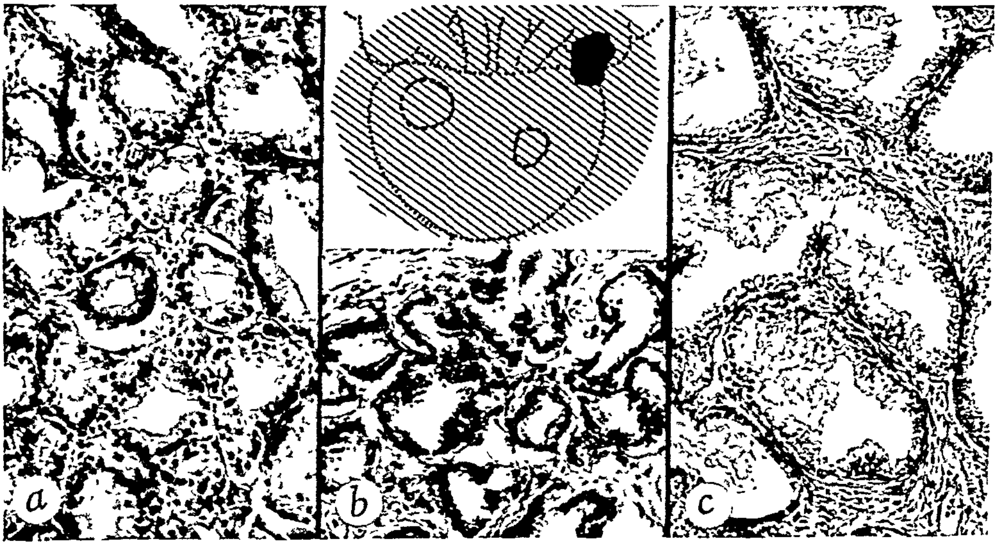

Fig. 8. Case 7. *Inset*, diagram of enlarged prostate showing hard nodule near base of right lobe, and sites of biopsy of left lateral lobe and right side of posterior lamella. *a*, Photomicrograph of biopsy specimen taken from center of enucleated left lateral lobe showing carcinoma (hematoxylin and eosin; ×150). *b*, Photomicrograph of biopsy specimen taken from right side of posterior lamella showing adenocarcinoma (hematoxylin and eosin; ×150). *c*, Photomicrograph of biopsy specimen taken from palpable nodule showing benign hyperplasia (hematoxylin and eosin; ×100).

Case 4 A patient, aged 63, had a smooth, movable nodule in the right lateral lobe which was examined annually for eleven years Between the 1951 and 1952 examinations it became larger and firmer Frozen-section examination disclosed adenocarcinoma (fig 5)

Case 5 offers irrefutable proof that the degree of induration can be a fallacious index and that more prostates should be subjected to biopsy

Case 5 A rather ill defined nodule, only slightly firmer than the remainder of the gland, was noted in a patient aged 63 Most examiners interpreted it as a small adenoma Frozen section examination showed adenocarcinoma (fig 6) Four similar doubtful lesions proved to be adenocarcinomas

The elusiveness of prostatic cancer and the importance of multiple biopsies are demonstrated by cases 6 and 7

Case 6 A patient, aged 69, had prostatic enlargement and typical obstructive symptoms The right lobe contained an extremely hard nodule Frozen section examination disclosed only benign hyperplasia A similar but random biopsy of the unsuspected left side of the gland revealed adenocarcinoma (fig 7)

Case 7 A patient, 70 years of age, had severe obstructive symptoms At the base of the right lobe of the prostate there was a very firm nodule Frozen-section examination showed benign hyperplasia The enlarged lateral lobes were enucleated Routine frozen section examination of the specimen revealed an unsuspected carcinoma within the tissue from the left lobe The remainder of the prostate was removed and a second area of adenocarcinoma was found in the posterior lamella (fig 8) Perhaps multicentric growths of this type account for some of the conflicting opinions regarding the behavior of so called occult lesions

SUMMARY AND CONCLUSIONS

In 45 cases no discrepancies were encountered between diagnoses based on frozen sections obtained by direct perineal biopsy and those made after study of permanent sections from the same tissues If frozen-section biopsy had not been performed, 5 patients would have lost their entire prostates needlessly and would have been destined to be impotent, while 5 other patients with true carcinomas probably would have had no operation If multiple biopsy specimens had not been examined, 2 additional patients would have been left with carcinoma after simple enucleation The results of this study, therefore, seem to warrant the following conclusions

Carcinoma of the prostate can be diagnosed with consistent accuracy from frozen sections, providing the biopsy is adequate Difficulties with the method are probably due to inexperience

To initiate or deny irreversible, definitive therapy solely because of impressions derived from the palpation of the prostate is fraught with considerable hazard Not all nodules of third degree induration are malignant and many carcinomas are only slightly indurated Histologic confirmation of clinical diagnoses is imperative if radical prostatectomy is to be employed judiciously

The combination of direct frozen section biopsy and simultaneous radical perineal prostatectomy, when indicated, still seems to be the logical treatment for early carcinoma of the prostate

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METHODS OF DIAGNOSIS OF CARCINOMA OF THE PROSTATE: A COMPARISON OF CLINICAL IMPRESSION, PROSTATIC SMEAR, NEEDLE BIOPSY, OPEN PERINEAL BIOPSY AND TRANSURETHRAL BIOPSY

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Carcinoma of the prostate is a disease which produces no symptoms in its early stages, yet it kills thousands of patients every year because early diagnosis and appropriate total excision are rare. The detection of early carcinoma depends upon frequent intelligent palpation of the prostate in men over forty plus a high index of suspicion of any induration and biopsy of equivocal areas.[1, 2]

This study was undertaken to evaluate the diagnostic accuracy of digital rectal examination, prostatic smear, and needle biopsy in 99 cases representing various stages of suspected carcinoma of the prostate. In all patients the diagnosis was confirmed by open perineal biopsy, or after transurethral resection in advanced cases. The study shows that needle biopsy properly performed under local anesthesia is a practical and extremely useful technique of diagnosis.

The consensus has been that rectal examination by an experienced clinician is the best diagnostic tool short of open surgical biopsy. Our inquiry emphasizes the importance of this practice.

The important work of Papanicolaou and Traut[3] in diagnosing carcinoma from the examination of exfoliated cells gave hope that this would provide a simple means of detecting early prostatic malignancy. Although many investigators were originally enthusiastic, the majority of them now feel that the method is unsatisfactory in disclosing early carcinoma.[4, 5, 6] However, in late, untreated cases and in experienced hands, it is generally agreed that there is an 80 to 90 per cent positive correlation between the smear findings and the pathological diagnosis.[7, 8]

Although punch biopsy of the prostate has been practised for many years,[9, 10]

Note by editor. The Joseph F. McCarthy prize essay.

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* Pathologist, Culver City Hospital, Culver City, Calif. (Dr. Rosenthal was responsible for interpreting the prostatic smears in this study. The routine pathology was performed by the Department of Pathology, Veterans Administration Center, Los Angeles, Calif.)

[1] Hinman, F., Jr.: Calif. Med., **68:** 338–343, 1948.

[2] Kimbrough, J. C. and Rowe, R. B.: J. Urol., **66:** 373–378, 1951.

[3] Papinicolaou, G. N. and Traut, H. F.: New York: The Commonwealth Fund, 1943.

[4] Boyer, W. F.: The cytological diagnosis of prostatic carcinoma. Proc. of Second Nat'l Cancer Conference, Cincinnati, March 1952.

[5] Herbut, P. A. and Lubin, E. N.: J. Urol., **57:** 542–551, 1947.

[6] Hunter, W. C. and Richardson, H. L.: Surg., Gynec., & Obst., **85:** 275–280, 1947.

[7] Albers, D. D., McDonald, J. R. and Thompson, G. J.: J.A.M.A., **139:** 299–303, 1949.

[8] Peters, H.: J. Urol., **66:** 770–777, 1951.

[9] Barringer, B. S.: Surg., Gynec., & Obst., **34:** 168–176, 1922.

[10] Ferguson, R. S.: J. Urol., **37:** 774–782, 1937.

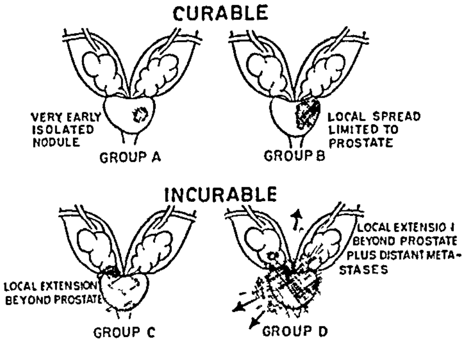
CURABLE
VERY EARLY ISOLATED NODULE
GROUP A
LOCAL SPREAD LIMITED TO PROSTATE
GROUP B
INCURABLE
LOCAL EXTENSION BEYOND PROSTATE
GROUP C
LOCAL EXTENSION BEYOND PROSTATE PLUS DISTANT METASTASES
GROUP D

FIG 1 Classification of cancer of the prostate

it has never become popular There are several reports which show a degree of accuracy for this method which approaches 95 per cent in cases where the clinical diagnosis is reasonably certain [11, 12, 13] Still, most urologists feel that it is inadequate for anything but occasional confirmation of large lesions [14, 15]

This study appraises these diagnostic methods using tissue obtained from open perineal biopsy or transurethral resection to establish their validity

METHODS

We have adopted a clinical classification of prostatic cancer shown in figure 1 Groups A and B represent disease still confined to the prostate and hence potentially curable by proper surgery Groups C and D represent advanced carcinoma, considered incurable by present methods

1) Clinical evaluation Interpretation of prostatic palpation is difficult to standardize We have graded the consistency of the prostate on the basis of 1 to 3 degrees, with 1° representing normal prostatic consistency, 2° indicating definite increased firmness often exemplified by fibrosis or isolated fibroadenomata, and 3° characterizing the stony hardness of prostatic carcinoma or calculi The subtle shadings between these categories are familiar to most clinicians Fixation of the prostate, obliteration of sulci, irregularity of contour of the gland and lateral ligament induration are criteria which, while subjective, are extremely important in determining the status of the neoplasm

For purposes of uniformity one of us examined and graphically recorded his impressions of digital rectal findings in all cases A pictorial record, no matter how individualized, is useful in the evaluation and subsequent re-evaluation of these patients Biopsies were performed whenever there was any question as to the nature of the prostatic induration Clinical impressions of palpatory findings

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[11] Rinker J R and Shuman, W G J Urol , 67 709–712, 1952
[12] Semple, J E Brit M J , 1 1236 1238, 1951
[13] Peirson, E L and Nickerson, D A New Eng J Med , 128 675–678, 1943
[14] Creevy, C D J A M A , 138 412–414, 1948
[15] Smith G G J Urol , 64 671–680, 1950

were classified as 1) carcinoma, 2) probable Carcinoma, 3) improbable Carcinoma. For purposes of conciseness Carcinoma and Probable Carcinoma are subsequently referred to as "Positive" and Improbable Carcinoma as "Negative" clinical impressions.

Cystoscopic findings and results of marrow aspiration, blood chemistries, and X-ray examinations are not included in the present data except as their implications helped to determine group D carcinoma when it was not otherwise suspected.

2) Prostatic smear. In 70 of 99 cases, exfoliated prostatic cells were examined. Expressed prostatic secretion was used in most instances. In some cases when massage was unproductive, the urine sediment after massage was examined. This is in accord with the belief that prostatic fluid is more likely to show diagnostic cells than urine sediment.[4] The Papanicolaou technique of fixation and staining was used.[3] Specimens for this type of examination were obtained in only 70 per cent of the total series. Indwelling catheters, unproductive massage, and occasional tenderness of the prostate were factors interfering wth smear examination in the other 30 per cent of cases.

Approximately 15 per cent of the smears were considered unsatisfactory because of the sparsity of cells. In 25 per cent the numbers of cells were meager and required prolonged scanning of the slides. This is attributed in some cases to an insufficient amount of prostatic fluid or to dearth of exfoliated cells. In other instances, it was apparent that many cells had been lost in the process of fixation and staining. Recently we have attempted to concentrate cells by digestion of the prostatic substrate followed by centrifugation of the freed cells in a tenacious mucus plug which is then smeared and fixed.[16] Our experience has been too limited to offer an opinion regarding the usefulness of this more complicated method. We are, however, encouraged to continue its use (fig. 2, *A*).

The literature is replete with references to the interpretation of exfoliated cytology and its discussion is superfluous here. Standard diagnostic criteria have been used; groups of cells of large size with nucleocytoplasmic disproportion and with variation in nuclear size, shape, and staining density (fig. 2, *B* and *C*). Caution must be used in interpreting seminal vesicle smears which may present cell atypism suggesting carcinoma to the neophyte.[8] In our series only a few patients had received previous hormonal therapy for carcinoma of the prostate, but it is in these cases that the cellular pattern may be distinctly altered with the finding of large squamous and vacuolated cells (fig. 2, *D*).[17, 18]

3) Needle biopsy. The Silverman biopsy needle was used almost exclusively in this series. We have had limited experience with some of the other instruments devised for this purpose (fig. 3, *A*).[19, 20] All have some shortcomings, and sufficient experience with one instrument seems to be prerequisite for obtaining specimens

[16] Rosenthal, M. and Traut, H. F.: Cancer, **4:** 147–149, 1951.

[17] Peters, H. and Benjamin, J. A.: Surg., Gynec., & Obst., **91:** 660–668, 1950.

[18] Rezek, P. R., Coplan, M. M., Woods, F. M. and Melvin, P. D.: J. Urol., **66:** 379–389, 1951.

[19] Melick, W. F.: J. Urol., **66:** 408–411, 1951.

[20] Veenema, R. J.: J. Urol., **69:** 320–322, 1953.

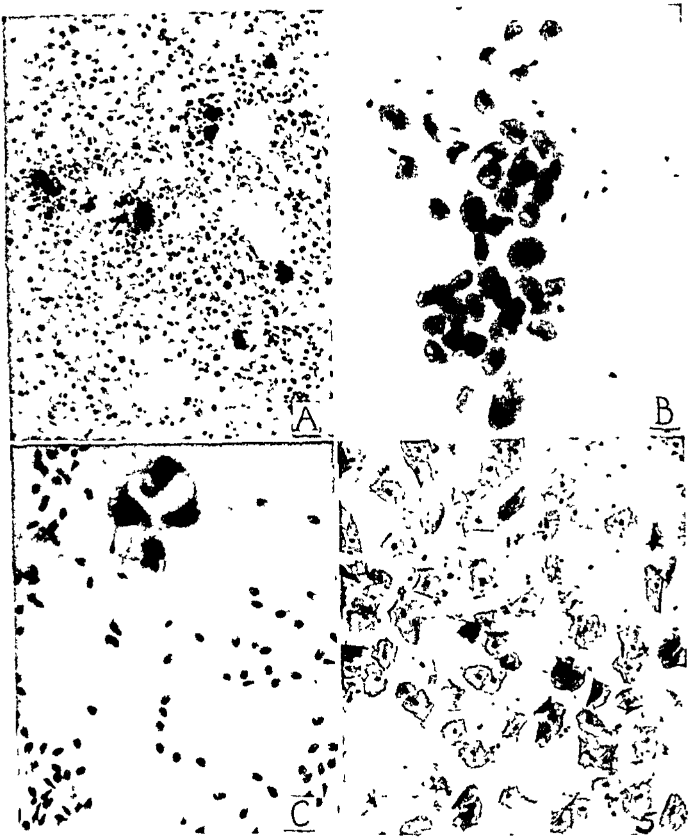

FIG. 2. *A*, concentrated prostatic smear showing several clusters of malignant cells in a single field (×150). *B*, group of prostatic carcinoma cells showing increased nucleocytoplasmic ratio and irregularity of nuclear size, shape, and staining density (×650). *C*, malignant cells arranged in aciniform pattern. Small cells are spermatozoa (×650). *D*, concentrated prostatic smear showing large squamous cells. Patient had been treated previously with estrogens (×350).

with any degree of regularity. Advantages of the Silverman needle are: It causes minimal trauma, and biopsy may easily be performed under local anesthesia as an office procedure; it is simply constructed; it is easily maneuverable and allows sensitive control with the rectal finger; it is efficient in obtaining adequate tissue once the technique is mastered. The chief disadvantage when compared with larger instruments is that tissue obtained is sometimes small and friable. With practice, however, cylinders of tissue which provide a good field for mi-

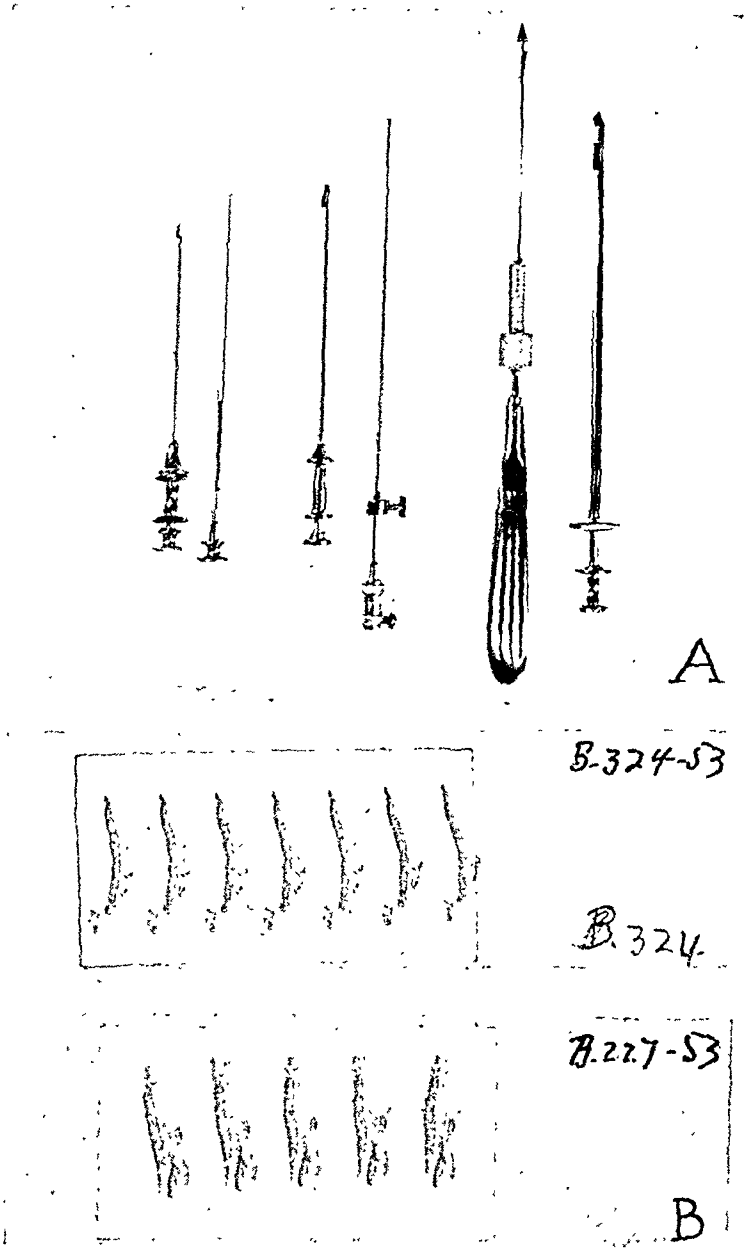

FIG. 3. *A*, prostatic biopsy instruments: Silverman needle, Turkel needle, Veenema punch, and Melick needle. *B*, microscope slides showing multiple sections of Silverman needle biopsies of prostate.

croscopic examination of multiple sections are obtained (figs. 3, *B* and 4). If the biopsy is taken from the critical area, the amount of tissue provided by this relatively small instrument is sufficient to make a diagnosis in most cases.

It was formerly our practice to use the needle with the patient anesthetized and in the exaggerated lithotomy position. A sound was placed in the urethra to depress the prostate. However, in the last 28 cases biopsy was performed under

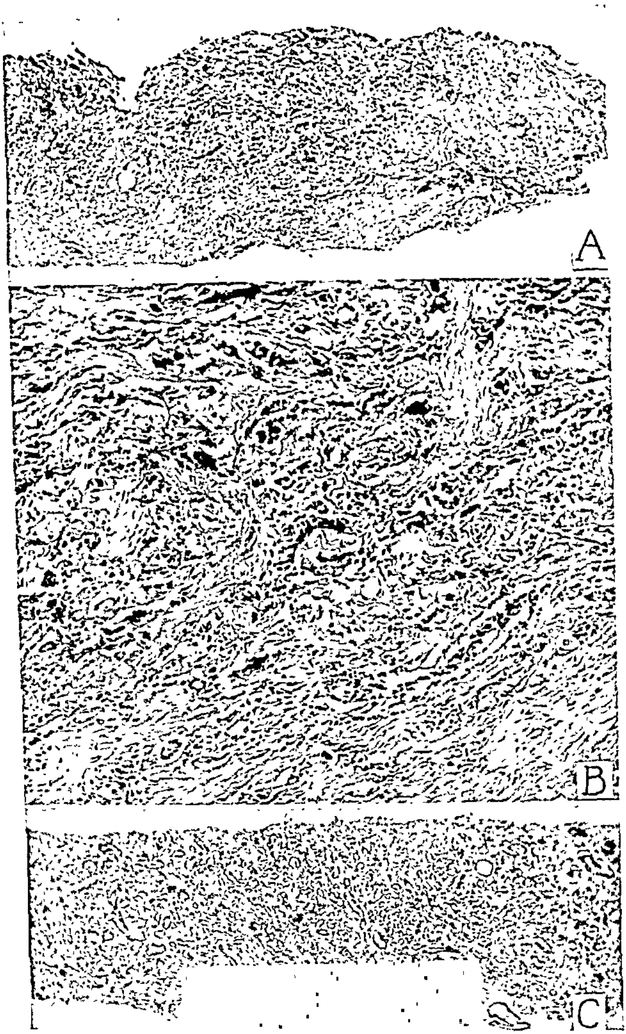

FIG. 4. *A*, low power photomicrograph of Silverman needle biopsy showing carcinoma (×100). *B*, high power photomicrograph of needle biopsy shown in *A* (×400). *C*, needle biopsy showing luxuriant prostatic carcinoma (×100).

local anesthesia with the patient in the ordinary lithotomy position and without a urethral sound. Trilene was used in some cases as a supplementary analgesic In these 28 cases the technique was as follows:

The needle is introduced low in the perineum, near the margin of the anus and a little to the right or left of the midline depending upon the location of the indurated area. The needle penetrates above or through the rectal sphincter and can be felt with the rectal finger for the entire distance as it is being advanced. By keeping the instrument just anterior to the rectum, the exact area of induration can be entered by depressing the outer end of the needle. In the earlier technique normal apical prostate was often penetrated before reaching a nodule at the base. This resulted in uncertainty about the position of the needle tip. An important feature of the method is the advancement of the needle and obturator up to the nodule but not into it. When the inner blades are advanced and extend beyond the end of the outer sheath they penetrate the nodule through its entire diameter and engage tissue from the desired area. The outer needle is then advanced for a distance of 2 to 3 centimeters while the inner blades are held stationary. The outer sheath is then rotated 360° (or the whole instrument is levered up and down) severing the cylinder of tissue at its base (fig. 5, *A*). Figure 5, *B* and *C* are low and high power photomicrographs of a needle biopsy specimen removed from a small nodule of the prostate (group A) by the method described and illustrated. The needle engaged carcinoma tissue proximally and fibromuscular stroma outside of the nodule beyond the carcinoma.

The biopsy can be done without assistance although it is helpful to have an assistant advance the outer sheath while the operator's finger remains within the rectum for additional biopsies.

If the inner blades can be withdrawn with ease, they are removed while the outer sheath is left in place. However, if resistance is encountered, blades and outer sheath are removed simultaneously. Since multiple biopsies are not significantly more traumatic, it is recommended that at least three good cylinders of tissue be removed for study.

4) Open perineal biopsy. This standard method of confirming the diagnosis of clinically suspected carcinoma of the prostate is the only means considered reliable by many urologists and pathologists. Open perineal biopsy was performed in 74 of our 99 cases. The classical Young or Belt's subsphincteric exposure was used. When the surgeon is familiar with the anatomy of the male perineum, the procedure is simple and almost free of complication. It can be done in one half hour or less in most cases. Extensive dissection about the prostate is unnecessary and undesirable. Generous wedge biopsies are taken from the suspected area as well as from other less suspicious areas (fig. 6).*

All of the biopsies in this series were subjected to careful microscopic investigation before the diagnosis of carcinoma was considered definite. Formerly multiple biopsies were submitted for rapid frozen section and radical prostatectomy was decided upon from their evaluation. Frequent difficulties in making a diagnosis from frozen sections have induced us to alter this practice in some cases.

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* Recently we have used the Castroviejo twin-blade knife for this purpose.

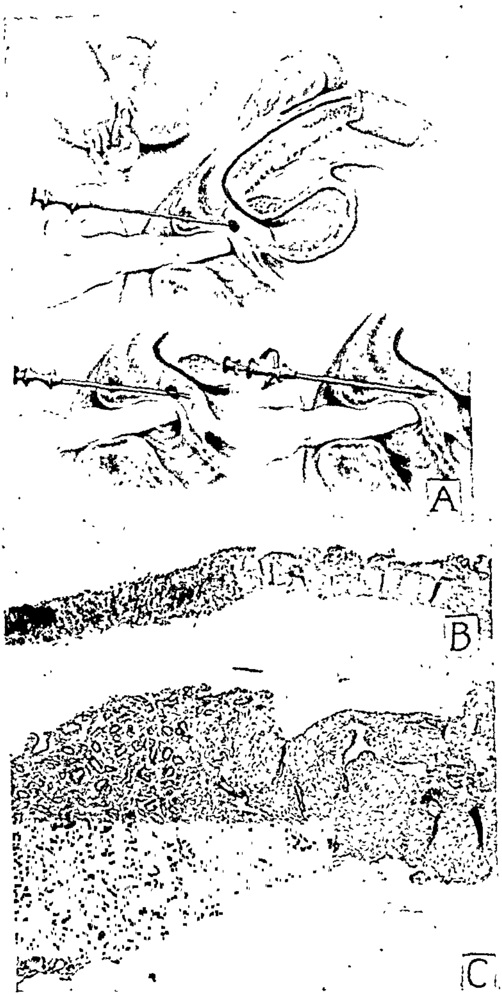

FIG. 5. *A*, artist's drawing of pararectal needle biopsy. Center: needle advanced up to, but not into, nodule. Lower left: obturator removed and biopsy blades advanced into nodule. Lower right: outer sheath advanced and rotated, severing cylinder of tissue at its base. *B*, needle biopsy confirming diagnosis of carcinoma in a small nodule of prostate. Cylinder of tissue contains carcinoma proximally and fibroadenoma distally (×20). *C*, higher power photomicrograph of specimen shown in *B*. Note sharp line of demarcation at border of carcinomatous nodule.

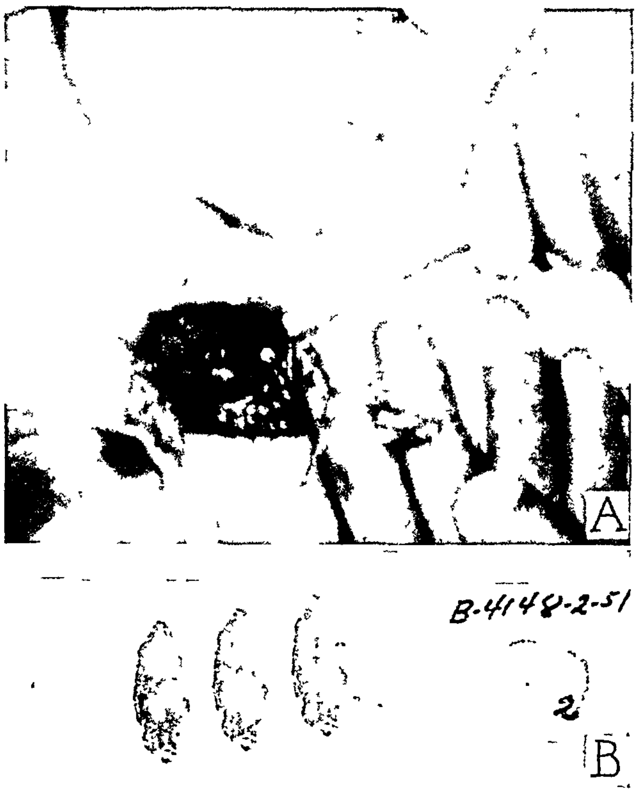

FIG 6. *A*, view of wedge biopsy just taken at open perineal exposure of prostate. *B*, microscopic slide showing size of open prostatic biopsy.

Several biopsies are submitted for multiple paraffin sections and detailed examination. The perineal wound is closed without further delay, and final disposition is made two or three days later when the permanent sections have been reviewed. Young's radical prostatectomy after previous perineal biopsy is as easy or easier than in unoperated cases, provided the operation is done soon after biopsy (2 to 7 days).[21] In the present series this was done on six occasions. It has been illuminating in several instances to find that carcinoma was present in biopsies taken from clinically unsuspected areas while the indurated area felt on digital rectal examination was devoid of tumor.

A distinct advantage of open perineal biopsy is that it affords important information concerning fixation of the prostate, knowledge of which will affect any decision regarding the feasibility of radical prostatectomy.† Five cases which were considered to be in groups A and B on the basis of digital rectal examination were found to have extraprostatic extension on perineal exposure of the gland. These were then treated conservatively.

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† When fixation is present, it is considered in this study to be a definite contraindication to total prostatectomy for purposes of cure In a determined effort to limit Young's radical prostatectomy to truly curable cases in this series, operation was performed in cases of groups A and B only (fig 1).[22]

[21] Goodwin, W. E.· J A.M.A., **148:** 799–803, 1952.

[22] Jewett, H. J.: J. Urol., **61:** 277–280, 1949.

5) *Transurethral resection* This has been practised only where the clinical findings indicated the need for alleviation of obstruction. The fact that the majority of tumors originate in the posterior portion of the prostate militates against the use of transurethral resection as a biopsy procedure in all but advanced cases. When the method has been used in conjunction with relief of obstructive changes, specimens taken from the posterior portion of the prostate are kept separate for microscopic study. Cuttings from other areas have been isolated for detailed examination when their gross appearance and consistency have suggested carcinoma.[23]

RESULTS

Three groups of comparisons have been made in this study. The standard (100 per cent) has been data obtained from open biopsy or positive transurethral biopsy. The results of clinical impression, prostatic smear and needle biopsy are compared with the results of surgical (open perineal or transurethral) biopsy.

Since the error in palpatory impression was in over-diagnosis of cancer, the percentage of accuracy is expressed in terms of $\frac{\text{Positive Surgical Biopsy}}{\text{Positive Clinical Impression}}$

Positive prostatic smears and needle biopsies can be compared more directly with the results of positive surgical biopsy in the following fashion:

$$\frac{\text{Positive Smear}}{\text{Positive Surgical Biopsy}} \text{ and } \frac{\text{Positive Needle Biopsy}}{\text{Positive Surgical Biopsy}}$$

The results are shown in table 1.

1) *Clinicopathological correlation* In groups C and D the clinicopathological correlations were 94 and 100 per cent respectively, with an average of 97 per cent. In groups A and B the correlations were 47 and 56 per cent respectively, with an average of 52 per cent.

Only one case of the 99 in this series was considered negative clinically and was proved to have carcinoma on biopsy. This was a case in group B and one in which the needle biopsy was positive.

Sixteen of the 99 cases in this series were considered negative on the basis of *clinical evaluation*. However, there were 35 negative *surgical biopsies* in the series with all of the clinical errors occurring in groups A and B. This indicates that the clinical error was in over-diagnosis of cancer and almost exclusively in the early carcinomas.

There were 11 suspicious smears in this series which were excluded from the positive figures since it was felt that they did not warrant a diagnosis of carcinoma. For a similar reason, four suspicious needle biopsies were excluded. The percentage accuracy figures therefore reflect only those smears and needle biopsies which were considered to show unequivocal carcinoma.

Nine unsatisfactory smears, so considered because of the sparsity of cells, were included in the correlation (and counted as negative values) even when their surgical biopsy counterparts were positive. This reduced the percentage of

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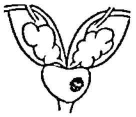
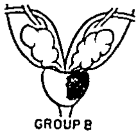
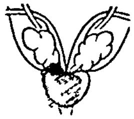
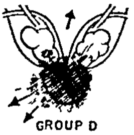
[23] Barnes, R. W., Bergman, R. T. and Farley, S. J. Urol., 57. 755–757, 1947

TABLE 1

	 GROUP A 27 CASES	 GROUP B 22 CASES	 GROUP C 35 CASES	 GROUP D 15 CASES
Positive open biopsy	7	9	18	6
Positive TUR	0	1	14	9
Total	*7*	*10*	*32*	*15*
Positive clinical impression	15	18	34	15
Accuracy	7/15 = *47%*	10/18 = *56%*	32/34 = *94%*	15/15 = *100%*
Positive prostatic smear	2*	1	8	9
Accuracy	1/6 = *17%*†	1/4 = *25%*‡	8/19 = *42%*§	9/10 = *90%*‖
Positive needle biopsy	5	5	23	13
Accuracy	5/7 = *71%*	5/10 = *50%*	23/32 = *72%*	13/15 = *90%*

* One false positive.
† Smear not done in 1 case proven positive on biopsy.
‡ Smear not done in 5 cases proven positive on biopsy.
§ Smear not done in 13 cases proven positive on biopsy.
‖ Smear not done in 6 cases proven positive on biopsy.

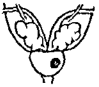
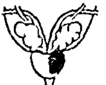
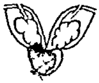
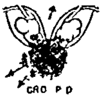
Overall Accuracy		*Accuracy in Groups A and B (Curable)*	
Clinical	74%	Clinical	52%
Smear	45%	Smear	21%
Needle	71%	Needle	61%

accuracy for the smear diagnosis. Similarly, seven needle biopsies containing inadequate prostatic tissue for evaluation, lessened the percentage of accuracy of the needle biopsy. These factors are considered equitable because unsatisfactory smears and needle biopsies are imperfections of the methods.

2) Smear-biopsy correlation. In advanced carcinoma (groups C and D) the correlation was 66 per cent, a figure which is somewhat lower than that achieved by other investigators.[4] In early carcinoma (groups A and B) the correlation was correspondingly lower (21 per cent). It is evident that higher correlations are obtainable in advanced carcinoma which invades the major prostatic ducts or urethra, but that poor comparisons occur when the tumor is small and still confined to the compressed periphery.

3) Needle biopsy-surgical biopsy correlation. The accuracy of needle biopsy was 81 per cent in advanced carcinoma whereas its accuracy was 61 per cent in groups A and B.

TABLE 2

	 GROUP A 7 CASES		 GROUP B 9 CASES		 GROUP C 10 CASES		 GROUP D 2 CASES	
	Pos	Neg	Pos	Neg	Pos	Neg	Pos	Neg
Surgical biopsy	3	4	3	4	9	1	2	0
Clinical impression	4	3	3*	4†	9	1	2	0
Needle biopsy	3	4	3	4	9	1	2	0

* One case clinically positive was negative on biopsy

† One case clinically negative was positive on biopsy

Clinical accuracy (28 cases)—90 per cent

Needle accuracy (28 cases)—100 per cent

The results of the last 28 needle biopsies are shown in table 2

These highly accurate results of needle biopsy are gratifying and although it is predicted that future biopsies will not continue to show such a precise correlation, we are encouraged by the improvement There are several factors which account for the recently improved results of needle biopsy They are experience, the pararectal approach, and multiple biopsies It is particularly rewarding that the diagnosis was made in six cases of curable carcinoma (groups A and B)

DISCUSSION

The most important factor in the present day diagnosis of carcinoma of the prostate is the palpatory finding of an area of unusual induration We have erred on the side of over suspicion and our mistakes were almost exclusively in groups A and B, properly so, as without suspicion there are no early cases and hence no cures

In this study prostatic smear examination has been less rewarding than needle biopsy in confirming the diagnosis of prostatic cancer Although a fairly high degree of correlation was achieved in the late cases, the results were poor in verifying early carcinoma Our series was too small, however, to warrant an accurate appraisal in this regard It is a method which requires pathologists who are experienced in the special techniques and interpretation and this lessens its popular value Despite the fact that it appears to be "second best" when compared to needle biopsy as a non operative means of confirming the diagnosis of suspected prostatic cancer, the true value of the method may still be in the detection of carcinoma in clinically unsuspected cases [8]*

Needle biopsy has given a high degree of correlation with the results of surgical biopsy in our last 28 cases The accuracy of the needle can be illustrated dramatically by the following case

R A (GH 37547) A 56 year old white man had a painless firm nodule about

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* The relatively poor results obtained from prostatic smear examinations in this study have led us to abandon further use of the Papanicolaou technique for this purpose

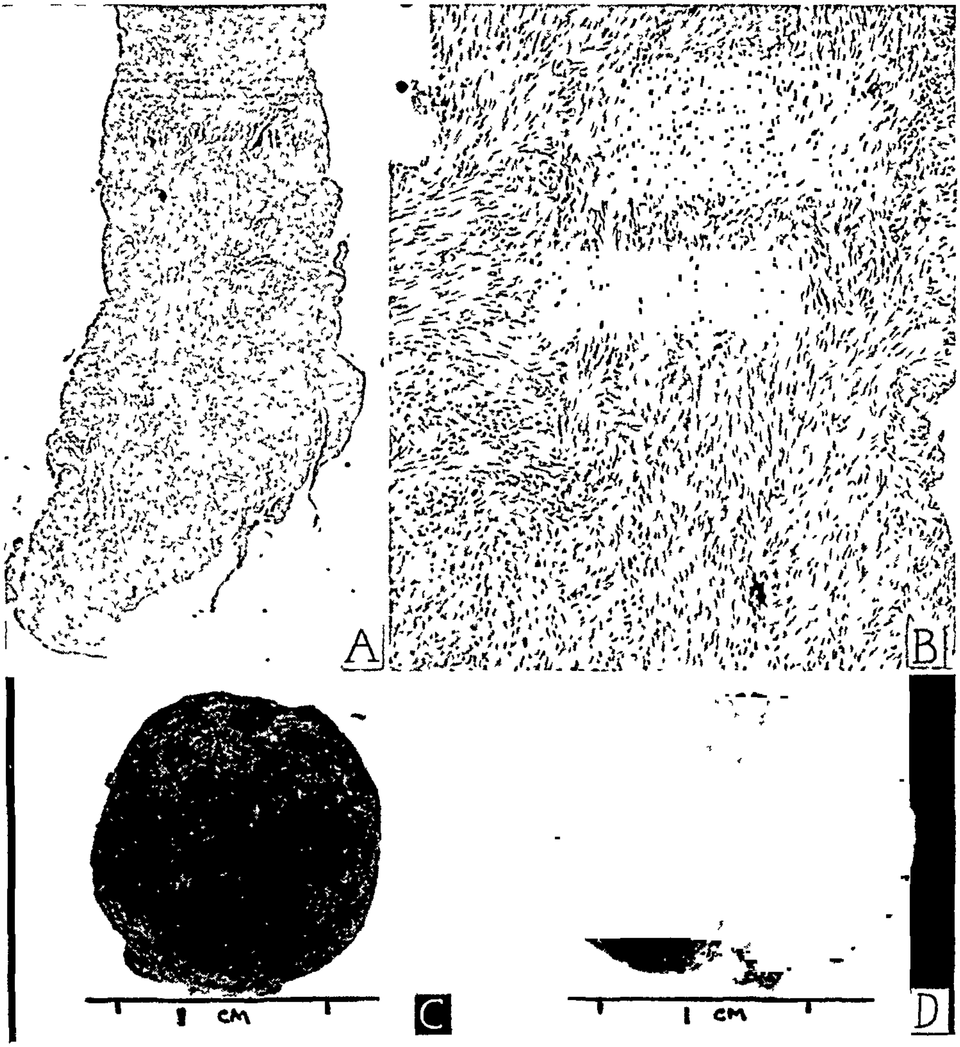

FIG. 7 *A*, needle biopsy taken from a small nodule of prostate. Tissue contains smooth muscle and is devoid of acinar elements (×100). *B*, high power view of biopsy seen in *A*. Note interweaving bundles of smooth muscle fibers and whorl formations. Preoperative diagnosis: leiomyoma of prostate (×400). *C*, leiomyoma shelled out after perineal exposure of prostate *D*, cut surface of leiomyoma showing "watered-silk" lustre.

one centimeter in size on the left lobe of the prostate which was considered to be carcinoma group A. He was otherwise asymptomatic; and bone survey, phosphatase studies, urinalysis, and cystoscopy were negative. Needle biopsy performed under local anesthesia revealed tissue suggestive of leiomyoma, composed of interweaving bundles and whorls of smooth muscle fibers and devoid of acinar elements and collagen (fig. 7, *A* and *B*). With this preoperative diagnosis, perineal exposure of the prostate was done and a leiomyoma measuring 1.3 centimeters in diameter was shelled out (fig. 7, *C* and *D*). This preoperative diagnosis is unique in the collected cases of leiomyoma of the prostate.[24]

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[24] Kaufman, J. J. and Berneike, R. R : J. Urol., **65:** 297–310, 1951.

Although there is a high degree of positive correlation between the *clinical impression* and the *surgical biopsy* data, needle biopsy is an important adjunct in the confirmation of the diagnosis of carcinoma of the prostate. It will not compete with open perineal biopsy as a means of ruling out carcinoma, but this does not detract from its other values. It is a procedure which can be done under local anesthesia in the office. It may be particularly helpful, when positive, for the urologist who is unfamiliar with perineal surgery. If a positive result is obtained in cases of groups A and B, one can proceed directly with radical prostatectomy either by perineal or retropubic approach depending upon the choice of the surgeon. If a positive result is obtained in groups C and D, and transurethral resection is not indicated for relief of obstruction, estrogen therapy with or without orchiectomy can be instituted with the assurance of a confirmed tissue diagnosis. It is in the latter groups also that positive diagnosis, achieved without recourse to surgical exposure of the prostate, will be of aid when injection of intraprostatic radioactive colloidal gold or chromic phosphate is considered for palliation. Also, it is a method which can be used when follow-up histologic examinations are desired to evaluate the effects of various palliative treatments in groups C and D (fig. 8, *A*).

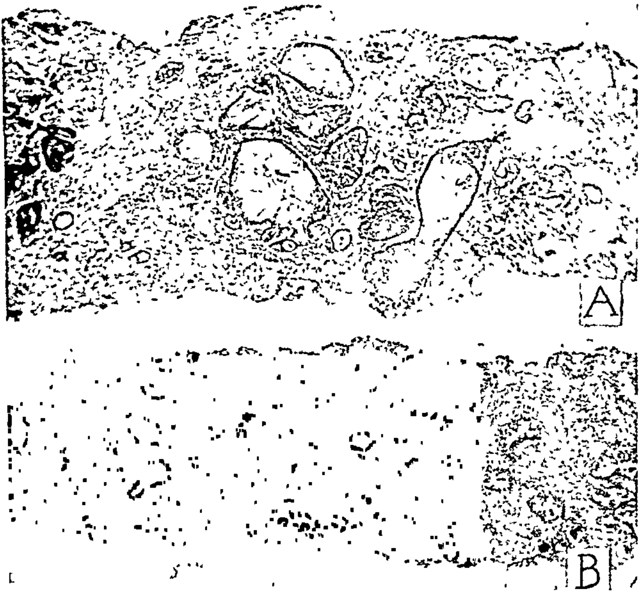

FIG 8 *A*, needle biopsy of prostate in patient previously treated with estrogens. Note squamous metaplasia of prostatic carcinoma. *B*, suspicious needle biopsy. Small compressed hyperchromatic acini are suggestive but not diagnostic of carcinoma (×80).

The greatest usefulness of needle biopsy is to obtain a positive tissue diagnosis in groups C and D. If a negative result is obtained, the urologist should repeat the procedure in two or three weeks. Since the treatment for curable prostatic cancer (Groups A and B) is total excision, open biopsy is still the procedure of choice for definitive diagnosis and treatment in those cases where the clinical diagnosis seems unequivocal. This is vastly preferable to the practise of administering estrogens as a "therapeutic test" and to surmise the presence of carcinoma on the basis of local softening or shrinkage.[15]

Some criticisms have been directed against needle biopsy of the prostate. These deserve mention and clarification. The possibility of implanting carcinoma in the path of the needle seems a remote problem in view of the fact that no such cases have been reported.* Dangers of rectal, bladder, or urethral injury resulting in fistula formation have caused concern to some urologists. In this series the rectum was accidentally entered three times, and the bladder was penetrated on 10 occasions with no untoward sequelae, despite the fact that no special measures were taken following their occurrence. Fort[25] and Grabstald[26] practise transrectal prostatic biopsies, which is further proof that rectal perforation in this procedure is of little consequence. The difficulties in making a positive tissue diagnosis from a needle biopsy specimen have been stressed. However, if several adequate cylinders are taken, sufficient tissue will be available for a pathological interpretation. There are occasional "borderline" cases which will not allow unequivocal diagnosis. However, this is true also of tissue removed by open biopsy and is often inherent in the character of the myriad forms taken by prostatic carcinoma. Specimens containing a few small, compressed atypical acini can only be called suspicious and will require additional needle biopsies, or ultimately open biopsies, for final clarification (fig. 8, *B*). In conclusion, we believe that needle or punch biopsy deserves further study and exploitation as a valuable measure in diagnosing both early and late carcinomas of the prostate.

SUMMARY AND CONCLUSION

Four methods available for the diagnosis of carcinoma of the prostate have been correlated. They are: palpatory findings, prostatic smear, needle biopsy, and open perineal or transurethral biopsy.

Ninety-nine cases of clinically suggestive carcinoma of the prostate were graded according to their degree of suspicion. All of these cases were subjected to needle biopsy and open perineal or transurethral biopsy. Seventy of the same cases had prostatic smear examinations.

Detailed description is given of the para-rectal needle biopsy of the prostate employing the Silverman needle.

A high degree of correlation (74 per cent) was demonstrated between the positive open perineal and transurethral biopsies and the clinical impression in both early and late cases There were many false positives on the basis of clinical impressions in cases suggesting early carcinoma of the prostate

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* A recent article by Clarke, B. G., Leadbetter, W. F. and Campbell, S. J. (J. Urol. 70: 937–939, 1953) reports the first recorded case of implantation of protastic carcinoma in the site of pernieal needle biopsy.

[25] Fort, A.: An. de cir., Rosario, **16:** 213, 1951.

[26] Grabstald, H. and Elliott, J. L.: J.A.M.A., **153:** 563–565, 1953.

The prostatic smear showed an overall positive correlation of 44 with the results of open perineal or transurethral biopsy Greater accuracy was obtained in the late cases An overall accuracy of 71 per cent was shown for needle biopsy when compared with the results of open or transurethral biopsy In the last 28 cases, including six early carcinomas, the needle accuracy was 100 per cent In these 28 cases the accuracy of palpatory impression was 90 per cent

The applicability of the various diagnostic methods in the confirmation of carcinoma of the prostate is discussed

It is concluded that with the rectal finger as a guide in discovering cases of carcinoma of the prostate, and with the biopsy needle as a confirmatory agent, a high degree of accuracy can be achieved in establishing the presence of prostatic cancer Positive diagnosis, thus attained, will often be helpful before instituting palliative treatment in late cases, and may be highly rewarding in disclosing early cases at a time when surgical cure is possible

ADDENDUM

Since this manuscript was submitted several comparable studies have been reported Two of these with results which closely parallel this study are the following Spring, W B and Alden, M W Canad M. A J 70. 179-185, 1954 Colby, F H Urol 69. 797-806, 1953

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TREATMENT OF PROSTATIC CARCINOMA WITH RADIOACTIVE COLLOIDAL CHROMIC PHOSPHATE (P^{32}): A PRELIMINARY REPORT

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It is the purpose of this report to evaluate the therapy and clinical results of the treatment of 28 cases of carcinoma of the prostate treated with colloidal radioactive chromic phosphate during the past year.

Radiation therapy by means of radium and roentgen rays has been used as a form of treatment over a period of many years for certain patients with inoperable prostatic carcinoma. The results reported by Pasteau, Young, Barringer, Deming, Bugbee, Bumpus, and others, included treatment techniques employing deep x-ray therapy externally, as well as the interstitial use of radium and radon alone or combined with external radiation. The prostatic cancer when radiated often showed definite reduction in the tumor mass. Occasionally complete eradication of disease has been reported. More recently when intensive x-ray and radium treatment was employed, most of the treated tumors showed some response. At the same time, with the larger x-ray and radium doses the incidence of complications resulting from the effects of radiation on the surrounding normal tissues increased in number and severity. Bladder irritation and ulceration and damage to the adjacent intestinal loops resulting in radiation colitis, ileitis, and sometimes stricture formation, made the necessary intensive x-ray and radium treatment for this condition impractical.

Flocks, Kerr, Elkins, and Culp (1952) have reported the results of treatment of this disease by the interstitial injection of radioactive gold (Au198). When such in colloidal solution was injected into the site of the prostatic cancer, the authors reported that 90 per cent of the material remained at the site of injection, and that it was apparently nontoxic. Improvements in technique seem to have done away with the moderate rectal irritation which they observed early in their studies. Local spread of the material is induced by the use of hyaluronidase, and the general spread by absorption into the blood is inhibited by epinephrin. One millicurie of radioactive gold per cubic centimeter of tissue represents approximately 65,000 equivalent roentgens of beta dosage together with some six to seven thousand units of gamma roentgens. Since the maximum range of the gold particle is only 3.8 mm. and because about 95 per cent of the effective rays are beta rays, very intensive irradiation of the tumor tissue is possible without danger of damage to the surrounding normal tissues. About one millicurie of colloidal gold-198 is injected into the prostatic area for each gram of estimated weight. This is accomplished by a special lead covered syringe with a rachet device per-

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Read at annual meeting, Western Section of American Urological Association, San Francisco, April 27–30, 1953.

mitting considerable pressure to be applied and at the same time limits the amount given to a volume as selected by the operator, ranging from 1 to 5 cc

The first 50 cases treated by these authors and followed from 7 to 17 months had previously been treated by hormones and other procedures without success The results as reported in the *Journal of Urology* (August, 1952) are as follows.

Average age	69
Previous treatment	29
Complications (all rectal)	15
Alive without clinical disease	27
Alive with clinical disease	8
Dead without clinical disease	7
Dead with clinical disease	8
Biopsies after Au	
Positive—27	
Negative—10	

We were impressed with the results reported by the University of Iowa group, but there were certain features of the gold treatment which we considered unsatisfactory First, the short half-life of radioactive gold (2 7 days) does not make it practical for shipping from the Atomic Energy Commission plant at Oak Ridge to the West Coast The second disadvantage of radioactive gold is the presence of gamma rays These probably do not add sufficient advantage for therapeutic purposes but do definitely present a health hazard to personnel handling the material because of their long range and high degree of penetrability This necessitates heavy lead shielding (32 lb lead pot necessary) in shipping, which increases the cost of air freight The gamma rays in radioactive gold also increase the need for shielding in the operating room while the material is being prepared by the radiologist It requires a special lead lined syringe for the surgeon in order to protect his hands To allow for the physical decay during shipping, it is necessary to order a larger quantity of the material This added quantity requires additional lead-shielding in shipping and further increases the cost of air freight The possibility of bone marrow depression by the gamma radiation is another disagreeable factor Recently, four cases have been reported by Botsford, Wheeler, Newton and Jaques (1953), where bone marrow depression occurred from doses of radioactive gold injected intraperitoneally and intrapleurally in ranges over 50 millicuries

We sought a radioactive substance that could be made in colloidal form with a particle size large enough so that it would not permeate the blood vessels and thus enter the general circulation We wanted a substance that would have pure beta radiation so that there would be little or no damage to adjacent normal structures and would require a minimal amount of shielding for shipping and safe handling in the operating room We desired to obtain a substance with a longer half life so that physical decay would not be rapid, and it might be possible to keep the material on hand for use as needed

Radioactive colloidal chromic phosphate seemed to fulfill all of these requirements It is made in the laboratory from the soluble form of radiophosphorus (P^{32}) It has a physical decay or half life of 14 3 days It is a pure beta ray emitter with energy of 0 7 million electron volts It has a range of 8 mm of maximum penetration in water or tissue, and it delivers a total dose in roentgen equivalents physical (REP) of 885,000 REP to 1 gm. or cubic centimeter of tissue containing 1 millicurie of the isotope completely disintegrating. The shielding required to protect the surgeon's hands is minimal since beta rays are easily filtered out by plastic, glass and aluminum. The rubber gloves worn by the operator are sufficient to protect the skin of his hands from contact with the beta rays. If there is any contamination of instruments, linen, operating room table or floor, the radioactive material may easily be washed off by means of a detergent soap and water. The handling of the patient postoperatively is safer because there are no long range gamma rays which may cause injury to visitors or to adjacent patients in wards. The effect in the tumor area is that of millions of beta particles of the material each acting as a radiation source which extends its effect over a distance of 8 mm. Theoretically, if one could distribute the material uniformly throughout the cancer area, it would be possible to destroy all of the cancer tissue without injuring the adjacent normal tissues.

Intensive radiation occurs in the immediate area of the injection of the isotope. However, the material may not be taken up by the lymphatics and delivered to the regional lymph nodes, as has been demonstrated with gold. It is questionable whether a lymph gland packed with tumor cells would receive additional radioactive material.

We have seen no deleterious effects from the use of this isotope as far as the general condition of the patient or the bone marrow is concerned. We have monitored the excreted urine and find that 1½ per cent of the injected material is excreted in 24 hours, and only an additional 1 per cent is excreted for the next 6 days. This shows that 97.5 per cent of the material stays at the site of injection. Samples of the patient's blood and bone marrow failed to reveal any radiation activity in these tissues. Very small amount of radiation could be picked up over the spleen, kidneys, and liver. This amount of radiation is not considered large enough to cause any damage to these organs.

When colloidal chromic phosphate was injected into the prostate of dogs, and they were sacrificed between 4 to 5 months, the following changes were noted. The entire prostate was reduced in size, the tissue was firm, avascular, and failed to show any radiation activity. The liver, spleen, kidneys, and lungs showed no deleterious effect or radiation activity. Sagittal sections through the prostate close to the site of the implanted radioactive material revealed scarring and inflammation with areas of necrosis. However, it was remarkable how restricted the effect was in the prostate. The histological examination disclosed a diffuse increase of fibrous connective tissue throughout the organ. The only tubules that showed any effect were in the immediate region of the implanted chemical (figs. 1 and 2, courtesy Dr. Harry Goldblatt). Microscopic sections on liver, kidney, spleen, lungs, and pelvic lymph glands showed no significant changes.

Patients with carcinoma of the prostate may be divided into three states of the disease, dependent upon the clinical findings: 1) when the cancer is limited to the prostate itself; 2) when the tumor extends beyond the prostatic capsule into the periprostatic tissue and regional lymph nodes; 3) when there are distant metastases. Unfortunately, the number of cases of carcinoma of the prostate in

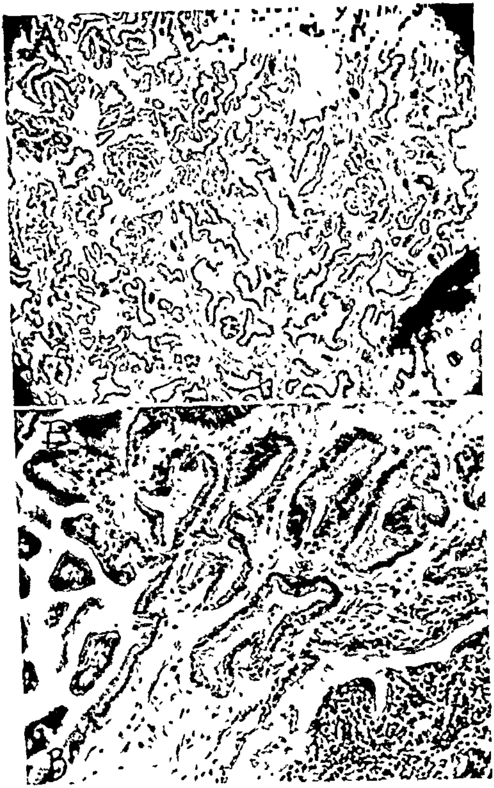

FIG. 1. *A*, low power photomicrograph of section of prostate of dog 1 cm. from site of injection. *B*, high power, same section.

stage one is small, approximately 5 per cent. In these patients the disease is discovered either by a routine rectal examination or at the time of transurethral resection. The treatment of choice in this stage is total prostatectomy.

A much larger number of patients present themselves in the second stage of the disease. Symptoms of bladder neck obstruction are usually present, and the examination reveals a fixation of the gland with extension of the lesion along the seminal vesicles. Occasionally regional lymph nodes are involved. However, no evidence of distant metastases are demonstrated. The treatment suggested in these cases has been transurethral prostatic-resection and hormonal therapy. Approximately 50 to 60 per cent of the patients with prostatic cancer present themselves in the second stage of the disease.

The patients seen in the third stage of the disease have all the findings of those

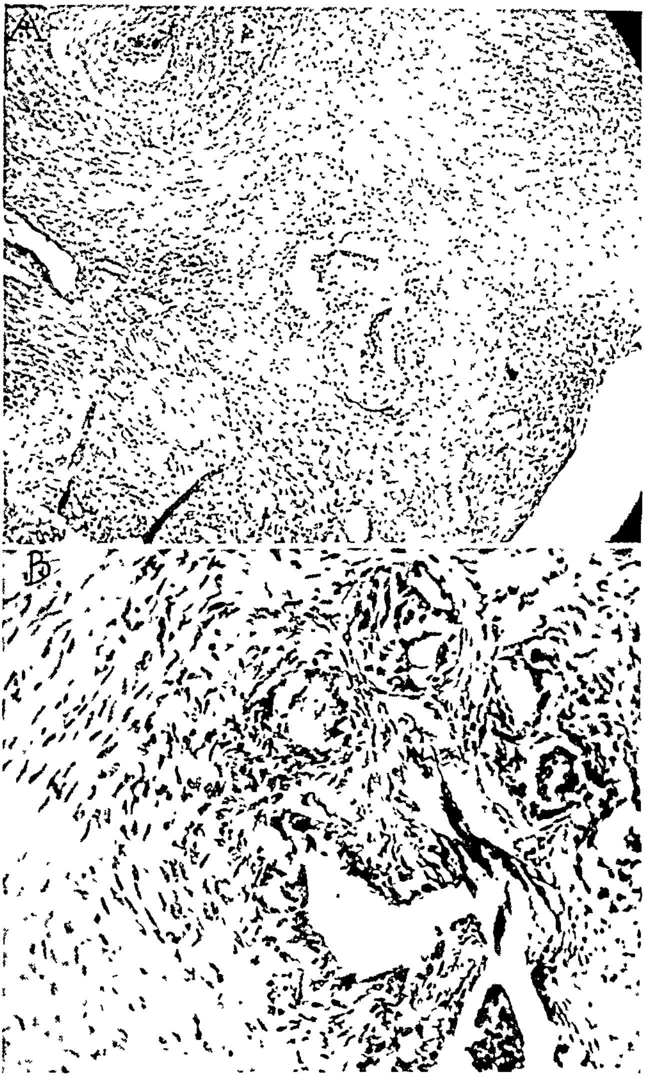

FIG. 2. *A*, low power photomicrograph of section of prostate of dog at site of injection. *B*, high power, same section.

in the second but in addition have distant metastases (osseous and lungs). The treatment in these patients has been transurethral resection of the bladder neck, estrogens, orchiectomy, and high voltage irradiation for relief of pain.

TECHNIQUE OF INJECTION

The perineal approach to the prostate for carrying out interstitial irradiation of the gland was found unsatisfactory because it does not permit adequate exposure of the prostate and the regional lymph nodes. However, it has been suggested that the prostate be injected from both approaches in order to obtain a more thorough distribution of the isotope. In three of the patients, metastatic masses 2 and 3 cm. in diameter were encountered. In only one was the mass removed. A biopsy was always taken of the involved nodes, and an attempt was made to thoroughly infiltrate all palpable nodes with the radioactive material.

It has been observed that in the smaller prostates the response has been better. Therefore, an increasingly larger amount of prostatic tissue has been removed transvesically before carrying out the injection, and the number of points of injection have also been increased.

After the bladder is opened a finger is placed in the rectum, making palpation of the prostate gland possible, to determine the local extension of the disease, the consistency and size of the prostate (weight in grams).

It is on this basis that the amount of radioactive material to be injected is calculated. A second biopsy of the prostate is always obtained at this time, and a revision of the bladder neck is carried out when obstruction is present. Multiple 21 caliber spinal puncture needles are inserted transvesically into the substance of the prostate, seminal vesicles, periprostatic tissues, and involved regional lymph nodes. The use of multiple needles has the advantage of obtaining more even distribution of the material, and in addition the immediate knowledge of direct entrance into a blood vessel, thus avoiding introducing of the material into the blood stream. Following the placing of the needles, the finger is removed from the rectum, making two hands available for manipulating the syringe, a distinct and welcome advantage. The radiologist is always in attendance to calculate and to prepare the material to be injected in each case. The solutions contain from 1 to 3 millicuries of chromic phosphate per cubic centimeter. To the isotope there is added 100 TU of hyaluronidase in 1 cc of 1:1000 epinephrine. Approximately 0.3 to 0.5 millicuries are injected for each gram of tissue; the largest amount injected in any single case was 40 millicuries.

A special syringe has been designed which permits the use of disposable glass

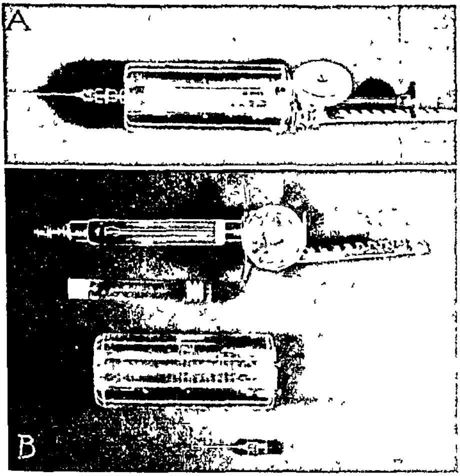

FIG. 3 Special syringe for injecting radioactive chromic phosphate into prostate. It is designed for use of disposable glass cartridges

cartridges. The material is packaged in these cartridges and therefore the loading of each syringe at the operating table is unnecessary. This minimizes the danger of contamination of the operator and operating room equipment. The syringe is shielded by a plastic cover which is adequate to filter out the beta rays (fig. 3).

The bladder is closed and drainage is maintained by an indwelling urethral catheter for 5 days.

The first 28 patients with cancer of the prostate who have been treated with chromic phosphate (P^{32}) are presented. The patients chosen for treatment were considered in stage two of the disease. With two exceptions they had all received estrogens from six months to two years. Eight cases had bilateral orchiectomies prior to treatment.

RESULTS

Ages of patients, from 54 to 81.

Symptoms: Bladder neck obstruction, 8; acute retention, 13.

Previous surgery: Transurethral prostatic resection, 13; bilateral orchiectomy, 8; permanent suprapubic cystostomy, 2.

Unilateral or bilateral extension to the seminal vesicles: 28.

Acid phosphotase: Elevated in 6.

Amount of radioactive material introduced: 6 to 40 mc. chromic phosphate (P^{32}).

Number of deaths: 4. Cardiac arrest, 1; pulmonary embolus, 1; coronary, 2.

CLINICAL COURSE

Change in size of prostate: None in 10; decrease in 18. Change in consistency of prostate: Softening, 4; firmer, 14. Postoperative biopsies: 3 months, 10; 12 months, 1.

Although sufficient time for detailed evaluation has not elapsed, the clinical results of treatment in this small group of cases have been interesting and encouraging. In 14 cases there was a remarkable decrease in the size of the gland and a definite change in consistency of the prostate within 30 to 60 days following treatment. Fifteen patients experienced a gain in weight and a general feeling of well-being. In 2 patients osseous metastases developed following treatment, one at six months, and the other at 4 months, respectively.

The microscopic findings are neither as striking nor as encouraging as the rectal and clinical findings. A biopsy with the perineal needle or transurethrally was obtained in all cases before treatment. A second was obtained transvesically at the time of injection of the isotope, and a third three to four months postoperatively. Tissue removed at 3 months was radioactive. Only ten of our patients have been treated more than six months, therefore postoperative biopsies have not been obtained in the other eighteen. In only one other case was a biopsy taken at 6 months. There was evidence of tumor in all biopsies. After a study of many sections in each patient, it was evident that there are histological changes in the radiated tissue when compared to the specimen of tumor obtained before treatment. Some sections revealed the presence of diffuse fibrosis and areas of necrosis. The nuclei of the malignant cells appear hypochromatic, irregular and shrunken, consistent with dying cells. However, in other areas in the same sections the tumor cells appear healthy and apparently are growing actively. The patient who has survived more than 12 months, is in excellent general health, without evidence of metastases. The prostate is small, firm, and fixed. The sections of tissue removed prior to treatment show epithelial cells arranged in strands, columns with small acini. *Diagnosis, adenocarcinoma (fig. 4). Sections of tissue* obtained at 3 and 6 months after interstitial radiation with chromic phosphate showed many areas of increased fibrosis, with areas of necrosis and inflammation. At 12 months there was extensive fibrosis throughout areas of the sections, and large masses of tumor cells revealed radiation changes. However, it is not possible to say from the histology that the tumor was destroyed in a single case (fig. 5).

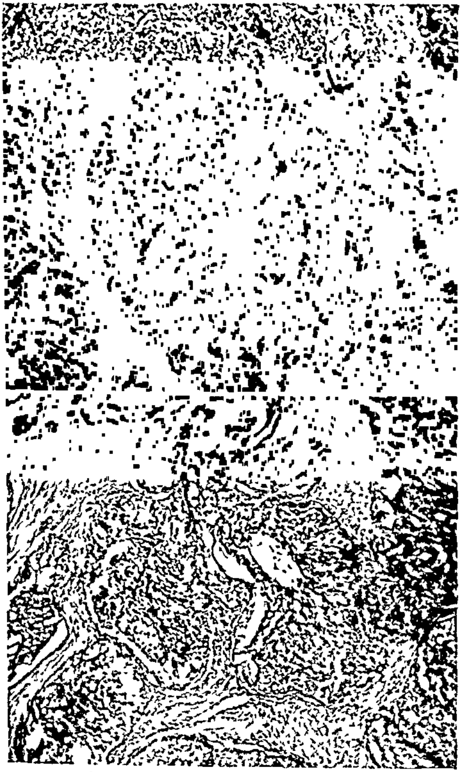

FIG. 4. *A*, low power photomicrograph of section of prostate, of patient alive over 12 months, prior to treatment. *B*, photomicrograph of a section of prostate, same patient, 3 months following treatment.

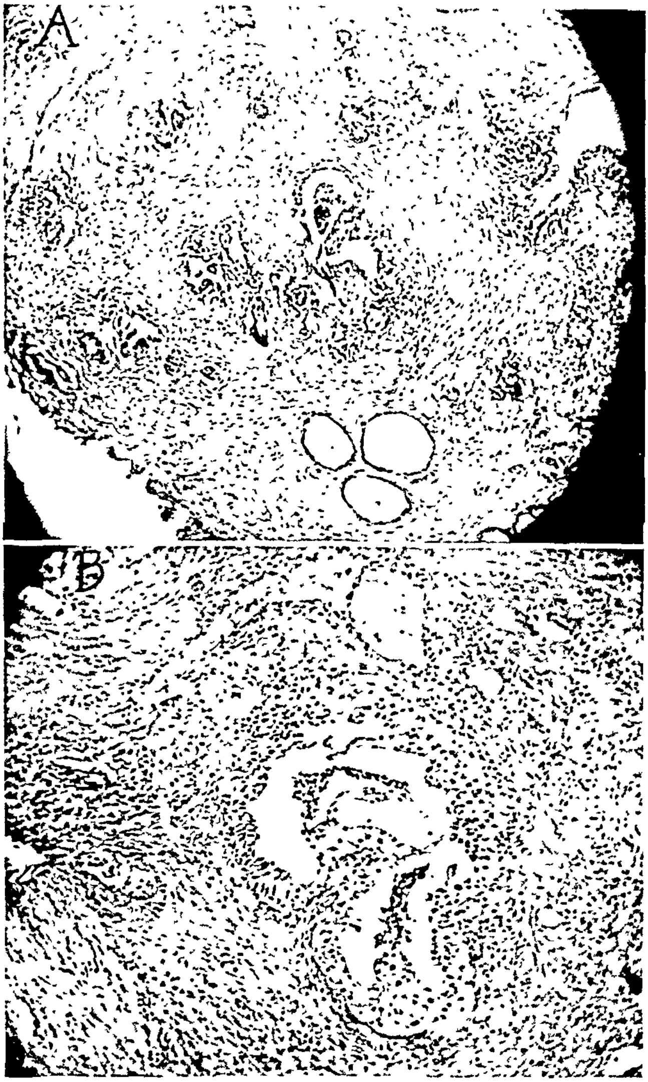

FIG. 5. *A*, low power photomicrograph of section of prostate, 12 months following treatment, showing marked fibrosis and atypical glandular formation. *B*, high power section reveals same advance radiation changes, but cells are present which can not be distinguished morphologically from tumor cells.

The marked scarring, necrosis, and diffuse fibrosis with the cellular changes which have been observed close to the site of the implanted radioactive material both in man and animal suggest that with thorough dispersion of radioactive chromic phosphate (P^{32}) throughout the organ, destruction of prostatic cancer should be obtained.

COMPLICATIONS

No serious complications have developed thus far. Some of the patients with edema of the rectal wall have complained of bowel irritation. Mild bladder symptoms have occurred in nearly all patients. These discomforts have subsided within 30 to 40 days. Immediate blood studies revealed a very small amount of material present, but there have been no late changes demonstrated in either blood or bone marrow. One patient, who died of pulmonary embolus after 5 days, showed radioactivity in the prostate and the associated pelvic tissues. The liver was radioactive. No evidence of radioactivity was noted in the spleen, kidneys, or lungs. An assay of the liver for the radioactivity content is being undertaken to determine the amount of material contained in this organ.

The authors wish to extend their gratitude to Mortimer E. Morton, Chief of Radioisotope Unit, Veterans Hospital, Long Beach, for his valued assistance and sedulous effort.

SUMMARY

Preliminary experience with the treatment of 28 cases of carcinoma of the prostate using colloidal radioactive chromic phosphate has been reported. Interstitial radiation of cancer of the prostate in stage two of the disease using radioactive isotopes emiting beta radiation, seems encouraging.

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INTRAPROSTATIC INJECTIONS OF RADIOACTIVE COLLOIDS: II. DISTRIBUTION WITHIN THE PROSTATE AND TISSUE CHANGES FOLLOWING INJECTION IN THE DOG

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The recent availability of radioactive materials has led the urologist to search for substances which would be effective in destroying or controlling neoplasms of the prostate gland and bladder.

Radioactive colloidal gold injections, as a therapeutic measure have been advocated by Flocks and Kerr.[1] Their preliminary reports offer sufficient encouragement to prompt further and more extensive investigation.

After inspecting some of the clinical work of Dr. Flocks at Iowa City, we felt that additional experimental work, using dogs, might be helpful in clarifying some of the unanswered aspects of this problem. Two phases of the problem seemed important. Since we were unable to find any published reports detailing the distribution and excretion of the radiocolloids following injection into the prostate gland, we felt it would be worth while to undertake such studies in dogs. The detailed findings of this study have been made the subject of another preliminary report.[2]

The present report is an attempt to record exactly what occurs locally in the prostatic tissue as well as in distant organs of the dog after injections of radiocolloids. Early and late tissue changes as well as distribution of the material within the prostatic capsule have been studied. Additional observations will be reported after a still longer period has elapsed.

Radioactive colloidal chromic phosphate (P^{32}) was used in these studies as well as radioactive colloidal gold (Au 198), since we felt that radioactive phosphorus offered several theoretical advantages.

Radiophosphorus, which has a half-life of 14.3 days and emits only beta particles with maximum energy of 1.7 m.e.v., has many advantages over radiogold which has a half-life of 2.7 days and emits 0.95 m.e.v. beta rays and 0.74 m.e.v. gamma rays. The absence of gamma rays makes the handling of radiophosphorus simpler and the radiological hazard to the personnel less. The longer half-life and higher energy of the beta rays of radioactive phosphorus result in a more prolonged and greater radiation than can be achieved with radiogold, using an equal concentration per gram of tissue. Complete disintegration of one

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TABLE 1 *Comparison of radiation delivered by radioactive phosphorus and radioactive gold*

	FRACTION OF DECAY IN FIRST 24 HOURS	EQUIV ROENTGENS DELIVERED IN FIRST 24 HOURS*	TOTAL EQUIV ROENTGENS DELIVERED*
Au 198	0.23	19.3	84
P 32	0.017	11.6	885

* These figures are calculated for a dose of 1 microcurie per gram of tissue to complete disintegration

microcurie of P^{32} per gram of tissue will deliver a radiation dose of 885 equivalent roentgens (e r), while the same amount of Au 198 will deliver only 76 e r of beta radiation The gamma ray contribution from gold is difficult to assess with certainty, but is of the order of 8 r per microcurie disintegrating[3] per gram of tissue Thus, it is possible to deliver approximately ten times the radiation dosage with radioactive phosphorus as compared with radioactive gold The range of the beta particles from radiophosphorus is about double that of radiogold The longer half-life of P^{32} permits a longer period of storage before use

The advantages of gold lie in whatever contribution the gamma radiation has to wider radiation of tissue For large doses of radiogold, the roentgens delivered to the gland by gamma rays alone may be in the cancericidal range This is important, if homogenous distribution in the gland cannot be achieved, since the effect of beta radiation is limited to a small volume surrounding the colloid The apparent greater uniformity and stability of the gold colloid and the lesser tendency to form larger aggregates may also be advantageous See table 1

METHODS

Ten dogs were injected with colloidal chromic phosphate and nine with colloidal gold The methods of injection and preparation of material are described in detail elsewhere[2] Animals were sacrificed at intervals of two weeks to three months in the case of phosphorus, and intervals of one week to seven weeks in the case of gold All organs were examined carefully both grossly and microscopically Tissues were prepared in the usual way, using paraffin embedding for sectioning and were stained with hematoxylin and eosin Fat stains were also done on the livers to detect possible liver damage The prostates injected with gold were also stained by the method of Elftman and Elftman[4] to better visualize the colloidal particles of this material Serial sections of the prostates were made in order to determine the distribution of colloid in all areas of the gland See figure 1

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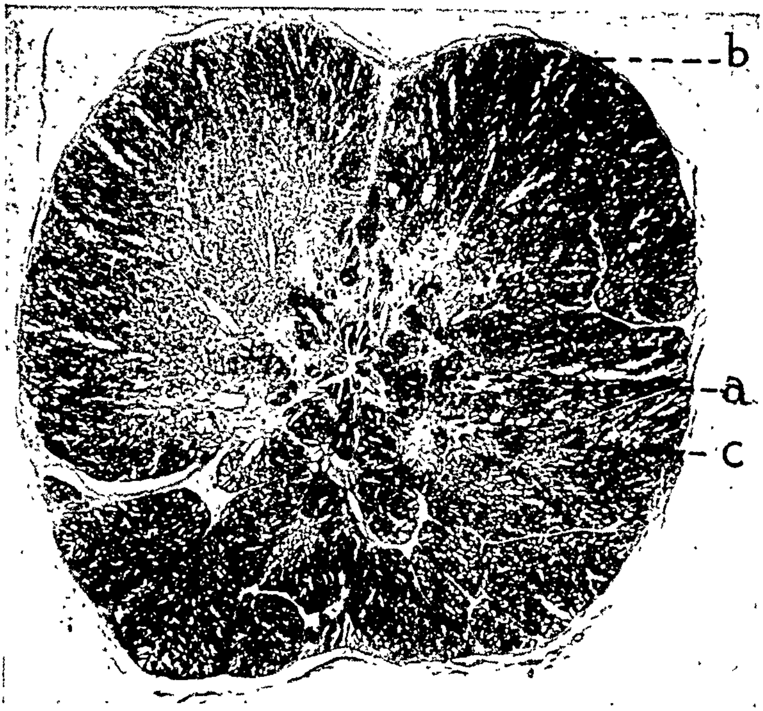

FIG. 1. Normal dog prostate

RESULTS

A. Radioactive colloidal chromic phosphate (P^{32}). The animals in this group showed no abnormal gross or microscopic findings except those to be described in the prostate gland and its investing layers. The regional lymph nodes were grossly unchanged and showed little, if any, radiation reaction.

There were a moderate number of periprostatic adhesions, more marked in the animals that had had extravasation of the radiogold at the time of injection. All of these adhesions were filmy and easily broken up by the finger. The prostate, itself, showed areas of subcapsular hemorrhagic reaction at two to five weeks. Serial sections of the gland revealed that the material had not been distributed uniformly throughout the tissue as we had hoped it might be, but that large areas of the gland were completely free of change. This was true in all of the prostates examined in spite of efforts to reach every part of the gland by the injecting needle.

Microscopically (figs. 2, 3 and 4), the reaction to radiophosphorus was marked first by acute necrosis, moderate hemorrhage and slight exudative reaction. The necrosis involved both fibrous and connective tissue as well as epithelial elements. The vessels showed a proliferative intimal arteritis with necrosis of the wall. This acute radiation reaction was very effective in destroying tissue, but it was even more apparent microscopically that much of the normal prostatic tissue remained unchanged. The acute reaction subsided after five to six weeks and healing became apparent at this time, and was fairly complete at the end

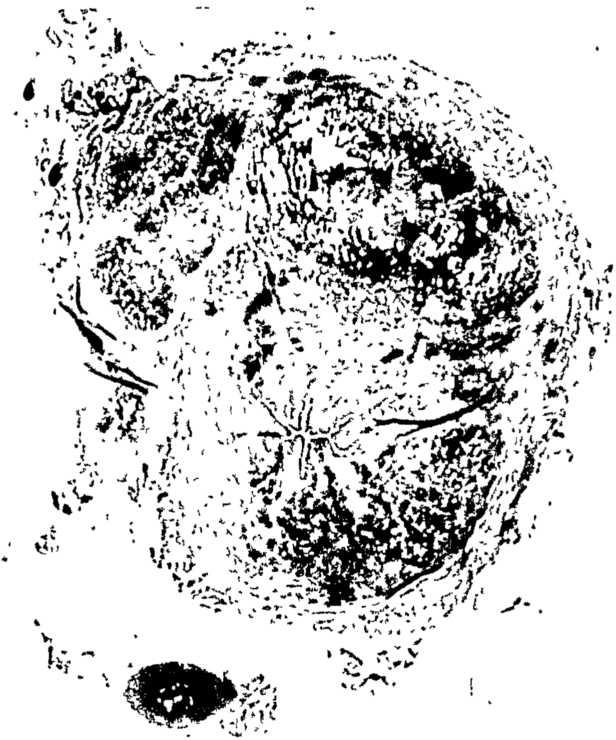

FIG. 2 Dog No 1, five weeks after injection Acute necrosis and hemorrhage following injection of radioactive phosphorus Note incomplete distribution

of three months. Healing by scar formation gave the picture of increased connective tissue, decreased or absent glands, pigmentation, cystic dilatation of nearby glands, and, in some areas, hyalinization. We were able to find normal glands in the center of an area of hyalinization in several cases, indicating that destruction had not been complete even in the center of the most marked radiation reaction.

B. Radioactive colloidal gold (Au 198). The animals in this group showed a much more marked periprostatic reaction as well as evidence of radiation effect in the regional lymph nodes. The dogs sacrificed at one and two weeks showed considerable edema of the periprostatic fat and enlarged hemorrhagic iliac lymph nodes. Those sacrificed at four and seven weeks had firm fibrous adhesions to the prostate and the gland was removed with difficulty for this reason. The lymph node change was quite prominent in this group. In the dogs injected with radiophosphorus, we had difficulty at autopsy in finding suitable regional nodes

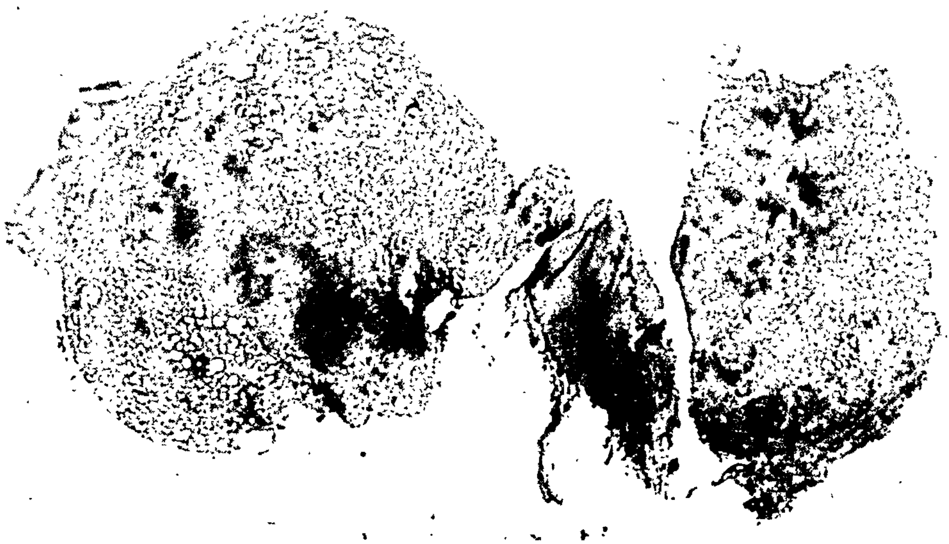

FIG. 3. Dog No. 6, two weeks after injection. Section showing acute radiation reaction to P 32 in a definite path through center of gland.

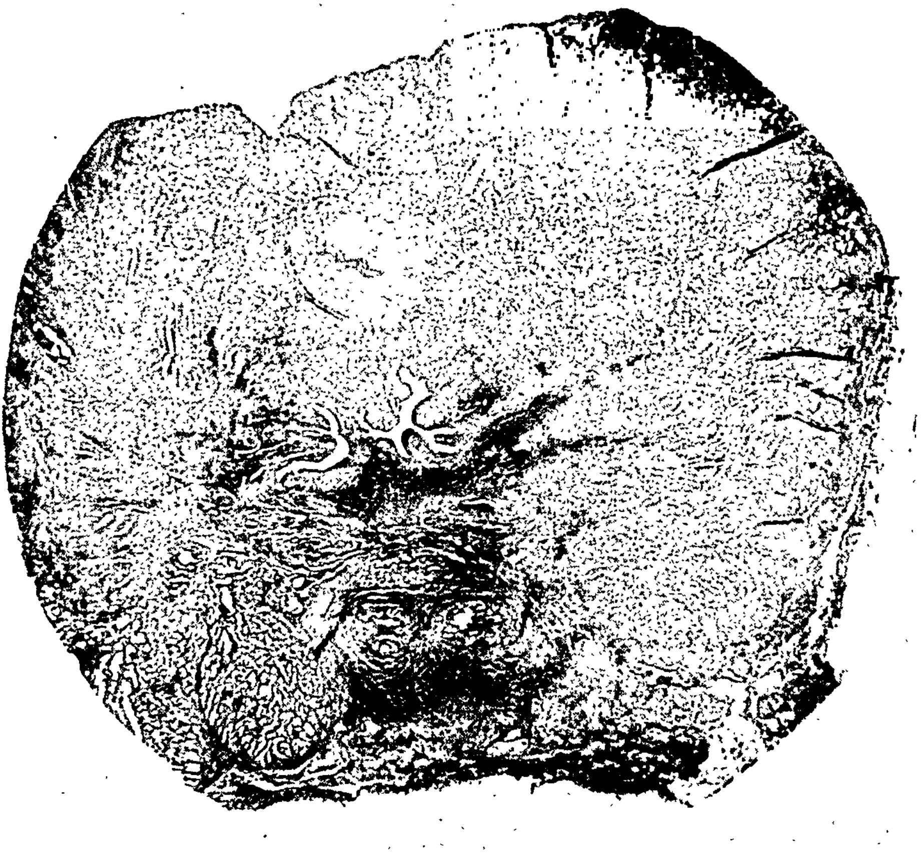

FIG. 4. Dog. No. 3, three months after injection of P 32. Section to show healed lesion with hyalinization and fibrosis. Note normal prostatic glands still present.

of any size for section, but, in the dogs injected with radiogold, these lymph nodes were enlarged two to three times, and, in most cases, hemorrhagic. Serial sections of the prostate, itself, showed a more marked capsular reaction, but about the same patchy pattern of distribution as we had observed in the case of radioactive phosphorus.

Microscopically (figs. 5 and 6), the acute reaction to radioactive gold was quite different from that observed in the previous group. Sections of prostates removed at one and two weeks showed an acute suppurative reaction with exudate in the glands and connective tissue. There were only small areas of hemorrhage and

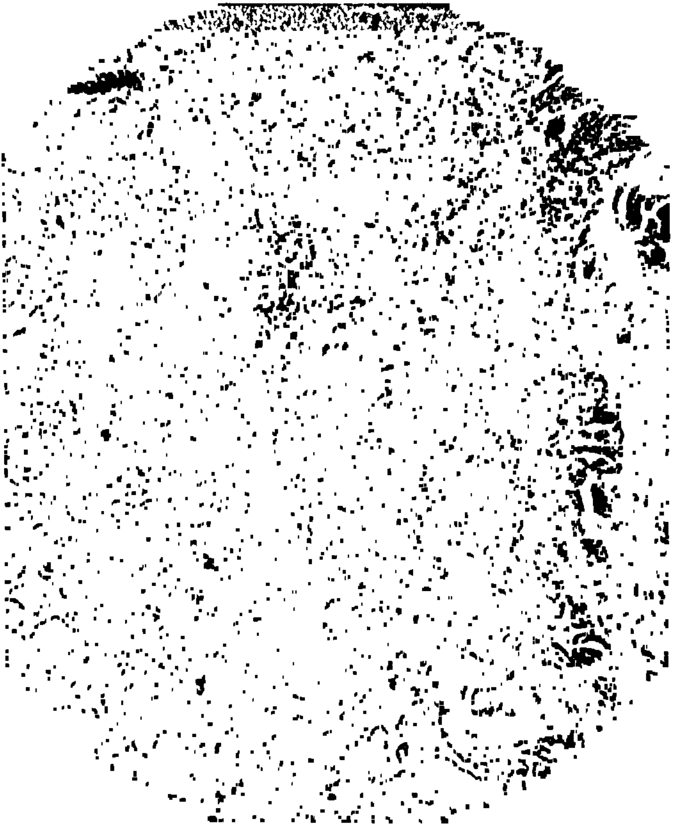

FIG. 5. Dog. No. 14, one month following injection of Au 198. Section to show acute radiation reaction resulting from injection of radioactive gold. Note exudative type reaction as contrasted with figure 2.

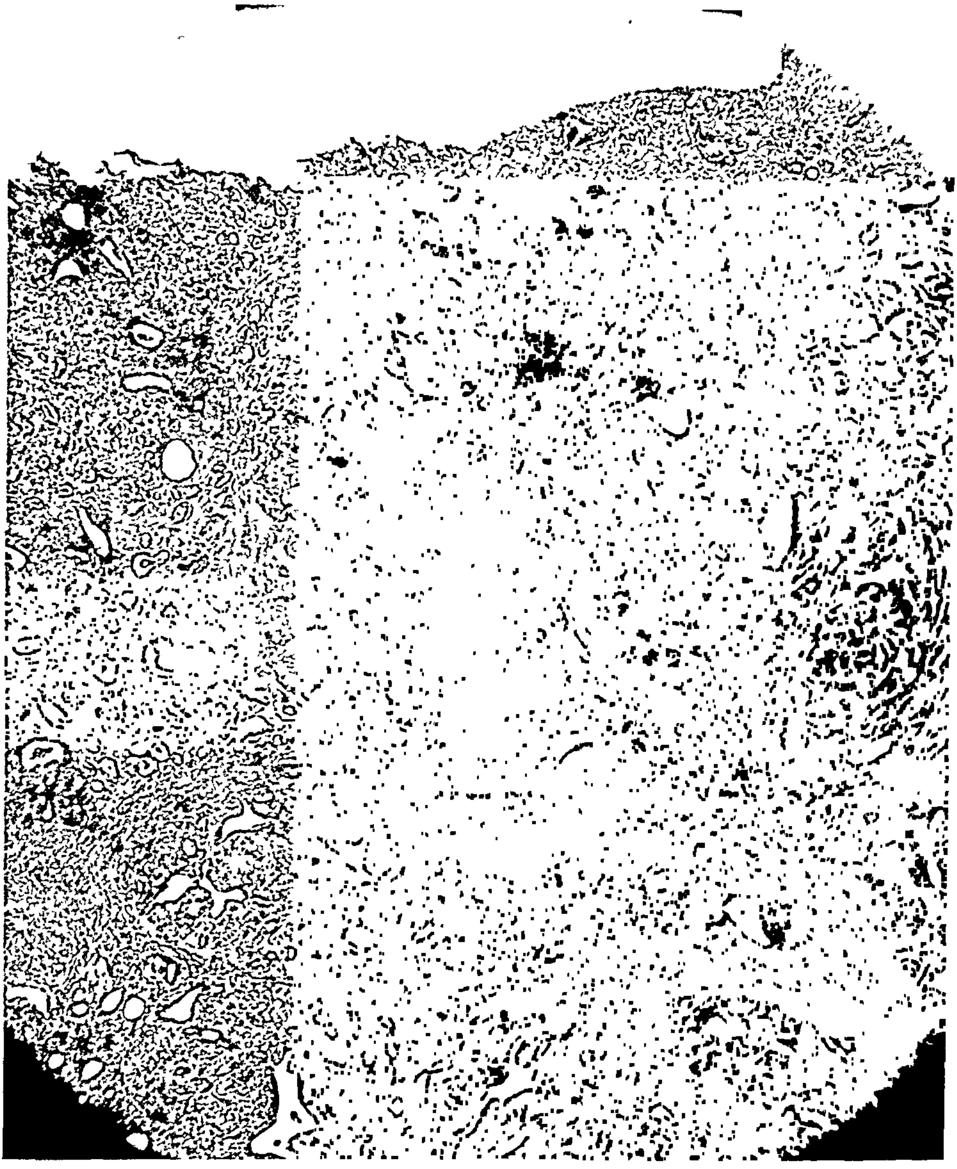

FIG. 6. Dog No. 13, seven weeks following injection of radioactive gold. Section to show late result following injection of radioactive gold. Area of scar surrounded by normal prostatic gland.

necrosis. The peritoneal reaction was more marked. The entire picture was that of an acute exudative reaction, and, at first, we thought we were dealing with a bacterial prostatitis. However, this suppurative type of reaction was a constant finding in all the five animals sacrificed at one and two weeks, and we feel that it represents the radiation reaction to the radioactive colloidal gold Later results, microscopically, were very similar to those observed with phosphorus. Healing took place by scar formation with an increase in connective tissue which replaced the glands destroyed. Again we were able to find normal glands in the midst of this scar tissue, indicating that the radiation effect had not been sufficient to destroy all of the prostatic glands, even where one would expect a maximum effect

The liver and spleen showed no microscopic change in spite of the pickup of considerable radioactive material[2] Other tissues were also unchanged grossly and microscopically

DISCUSSION

It became apparent early in this study that our main problem was to achieve equal and uniform distribution of the colloidal material throughout the prostate gland In the case of both radioactive gold and phosphorus, there was found to be little diffusion away from the path of the needle in spite of the addition of relatively large amounts of hyaluronidase and attempts to improve the technique by moving the needle to all sections of the gland The material in many cases had apparently diffused out into the subcapsular space so that we found a marked capsular radiation reaction and periprostatitis, but many areas of prostate entirely free of change Since many of the prostates weighed only five to ten grams, and were easily accessible at the time of injection, we had expected to achieve a fairly complete destruction of the entire prostate We estimated roughly that we had destroyed as little as 15 per cent of the total prostate gland in some animals and as much as 75 per cent in others, but in none of these animals had we achieved complete destruction of tissue within the prostatic capsule Flocks,[1] in his report on radioactive gold injected into human prostatic carcinoma, apparently experienced similar difficulties in distribution which he mentions in this report This lack of distribution in the human is also borne out by the fact that he has been able to show radiation effects in only about half of the biopsies made after injection of radiogold into prostatic carcinoma[5] It would seem from our studies on the dog that further efforts should be made to improve the technique of injection or the composition of the material, in order to insure a more complete distribution of the colloidal particles throughout the gland

The lack of demonstrable damage to liver, spleen or other organs, in spite of relatively large pickup of radioactive material,[2] would seem to indicate that the materials are safe to use locally without fear of serious side effects If a method can be devised to keep more of the radioactive material within the prostatic capsule, the possibility of damage to distant organs will be even less

The lymph node changes, both grossly and microscopically, were quite prominent with radioactive gold, and this may be a definite advantage to the use of gold in cases of carcinoma of the human prostate with lymphatic spread Little radiation change in the regional lymphatics was observed in the case of animals injected with radioactive phosphorus These observations were borne out by the findings of much greater radioactivity in regional lymph nodes of animals injected with radiogold[2]

The difference between the acute radiation effects of the two materials was quite striking Radioactive chromic phosphate caused an acute necrosis and

[5] Flocks, R H Personal communication

hemorrhagic reaction with little exudative reaction. Radioactive gold, on the other hand, caused an acute exudative reaction with little necrosis or hemorrhage. This difference is difficult to explain. The late reaction of tissue to the two materials was quite similar.

CONCLUSIONS

The injection of radioactive colloidal chromic phosphate (P^{32}) and radioactive colloidal gold (Au 198) into the prostate of the dog causes no appreciable radiation effect in organs distant from the prostate. The only exception to this statement occurred in the case of the regional lymphatics following the injection of radiogold.

Distribution of the colloidal material throughout the prostate was not uniform in any instance, and in none of these animals was destruction of the normal prostate complete. Periprostatic reaction was marked in the case of both materials, but more prominent following the injection of radioactive gold. When healing had occurred, large numbers of normal prostatic glands remained, and, in some cases, normal glands persisted within the center of the healed radiation scar. This was true following injection of both radioactive gold and radioactive chromic phosphate.

The acute radiation reaction occurring in the dog's prostate to radioactive phosphorus differs from that seen due to radioactive gold, but the long term result is about the same following injection of either material.

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CORTISONE TREATMENT IN ADVANCED CARCINOMA OF THE PROSTATE

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Intense interest has arisen in the role of the adrenal glands in carcinoma of the prostate, stimulated by Huggins' work with bilateral adrenalectomy [1] [2] [3]

In 1950, Sprague[4] in reviewing and discussing the physiologic effects of cortisone brought out, first, that cortisone causes a depression of the endogenous production of adrenal cortical hormone, second, that experimentally, cortisone causes atrophy of the adrenal cortices in rats and, third, that a depression of urinary 17-ketosteroids occurs with the administration of cortisone Wilkins et al [5] [6] demonstrated this clinically by showing excellent results with cortisone in children masculinized by congenital adrenal hyperplasia

It therefore seemed reasonable to us that the use of relatively large doses of cortisone in patients with advanced prostatic carcinoma might produce a "medical adrenalectomy" that could be as effective as actual surgical bilateral adrenalectomy We also believed that this would give us an opportunity to study some of the still unknown factors existing in the hormonal interrelationship present in prostatic cancer Taylor et al [7] [8] [9] in 1950 had reported on the use of ACTH and cortisone in a wide variety of malignancies including a few cases of prostatic cancer but no detailed and extensive studies of carcinoma of the prostate had been reported at the time we undertook this study Since then, there has been a case report in the literature[10] and more recently Harrison, Thorn,

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Read at annual meeting, Western Section of American Urological Association, San Francisco, April 27–30, 1953

Supported by Institutional Grant, American Cancer Society Cortisone acetate (Cortone) was generously supplied by Merck & Co Inc

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The acute radiation reaction occurring in the dog's prostate to radioactive phosphorus differs from that seen due to radioactive gold, but the long term result is about the same following injection of either material.

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3 *Acid and alkaline phosphatase findings* Four of the 10 patients initially had elevated serum acid phosphatase and 3 of these showed definite and consistent decrease, in one to normal levels Two of these patients had improvement in their local lesion but one of the two had no symptomatic improvement Two of the 10 had a marked progressive increase in acid phosphatase and yet both had wonderful symptomatic relief and improvement in their local lesion The remainder had no essential change in acid phosphatase Thus there seems to be no particular relationship between changes in the acid phosphatase and symptomatic improvement or change in the local lesion

Two of the patients with initially elevated levels of serum alkaline phosphatase had a definite and progressive increase, while the remainder had no essential change

4 *Improvement in bony metastases by x-ray* None of our patients showed improvement in their bony metastases, as determined by serial x-ray studies In fact, 6 actually had an increase in the number and size of metastases The others showed no real change

HORMONAL STUDIES

1 *17-Ketosteroid excretion* The excretion of 17-ketosteroids was followed in all of our patients Four of the 10 patients had a definite decrease in their urinary 17-ketosteroids In the others, all of whom had very low levels to begin with (below 2 mg /24 hrs) there was no change It is of interest that all but one patient had initial 17-ketosteroid levels of 1 1 mg /24 hrs or less, the exception having an initial level of 6 8 mg /24 hrs The relationship between changes in 17-ketosteroids and clinical improvement can be summarized as follows

Decrease in 17 ketosteroids and clinical improvement	4 cases
No change in 17 ketosteroids and clinical improvement	4 cases
No change in 17 ketosteroids and no clinical improvement	2 cases

2 *Protein bound iodine* Serial determinations of the protein-bound iodine as a measure of pituitary thyrotropic and thyroid function were done on 4 of our 10 patients All 4 showed a consistent and steady decrease from an average control level of 6 5 micrograms/100 cc to an average of 3 8 micrograms/100 cc This is consistent with reported results[13] [14]

3 *Pituitary gonadotropin excretion* (FSH + LH) The urinary excretion of gonadotropin was followed in 3 of the patients, with initial levels on 2 more In all 5, the reactions were initially zero The 3 patients which were followed had marked increases in gonadotropin excretion while on cortisone, their levels ranging between 80 and 220 M U /24 hrs This rise of gonadotropin during cortisone (and ACTH) therapy has been previously described during treatment of arthritis and other diseases[15]

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TABLE 1

PATIENT AGE	GOOD RESPONSE TO ORCHIECTOMY	DATE CORTISONE STARTED AND DOSE PER DAY (mg.)	SYMPTOMATIC CHANGE (SUBJECTIVE AND OBJECTIVE)	CHANGE IN LOCAL PROSTATIC LESION	ACID PHOSPHATASE	ALKALINE PHOSPHATASE	X-RAY METASTASES	17 KETOSTEROIDS	IMPROVEMENT		LENGTH OF REMISSION
									Subjective	Objective	
GW* 59	x	3-30-52 100	No decrease in pain. Some increase in appetite. No weight change	Complete disappearance of palpable prostatic tissue—originally there was stony hard 2 cm nodule.	Decreased 15 → 18 → 13 → 26 (KA)	Increased 29 → 37 → 55 → 73 → 96 (KA)	Increased	Low to begin (1.2 mg/24°) No change	0	x	None except local lesion and improvement in phosphatases. Bilateral adrenalectomy done
TC† 52	x	6-10-52 50 7-22-52 100 8-2-52 200 11-1-52 150	Complete relief of severe pain for 1 month with marked increase of appetite & 12 lb weight gain. Then mild intermittent pain for 1-2 days every 2 weeks. Improved urination	Complete disappearance of palpable prostatic tissue—was originally large, stony and nodular. After 5½ months began to reappear	Increased after 3 months, 1 → 6 → 11 → 22 (B)	Increased 6 → 11 → 13 → 15 (B)	Increased	Definite fall (1.1 → 1 mg/24°)	x	x	Six months. Bilateral adrenalectomy then done
ML 77	x	8-8-52 50	Tremendous improvement in strength, appetite. Loss of pain. 10 lb weight gain, ability to walk, increase of urinary stream.	Softening and shrinking of nodules. (At post, gland very small and soft.)	Slight increase 1 → 5 (B)	Decrease, then same 22 → 10 → 20 (B)	No change	Down (3.9 → 2 mg/24°)	x	x	Ten weeks. Died 10-26-52, bronchopneumonia
RS 76	x	8-3-52 50	Complete loss of pain in back and legs, allowing him to walk miles each day. Tremendous improvement in appetite—before severe anorexia. Weight gain 17 lb in 6 wks	Softening of gland with disappearance of nodularity. Smaller. Marked improvement in urination. Residual from 300 cc to less than 80 cc			Increased	Low to begin with (1.9 mg/24°) No change	x	x	Three months
GD 62	x	10-4-52 50 10-18-52 75	Increased appetite, decreased pain, increased strength. Able to get out of bed where before	No change	Increased then decreased, then slight increase	No change 11 → 20 → 24 → 18 (KA)	Increased in size. Collapsed vertebrae	Low to begin with (2.0 mg/24°) No change	x	0	2½ weeks

			He could not Decreased swelling of legs by measurement All very transient Collapsed vertebrae—paraplegia after 2½ weeks		18 → 50 → 12 → 32 (KA)					
HM† 55	x	8 18 52 50 10-9 52 100	Complete disappearance of pain, increase of strength and appetite	No change	Slight increase 0 8 → 2 6 (B)	No change 2 5 → 2 0 (B)	Increased (Developed path fracture of pubic ramus)	Not done Were 3 1 mg /24° before adrenalectomy	x	0	8 weeks Bilateral adrenalectomy done
BS 79	0	11-18 52 50 1 22 52 100	No change—only mild pain to begin with No improvement in weight or appetite or sense of well being	No change	Essentially unchanged 6 5 → 5 9 (KA)	No change 10 5 → 11 (KA)	No change	Low to begin with (1 0 mg /24°) No change	0	0	No remission
GN 67	x	11 24 52 50 1 14 53 100	Disappearance of severe pain & stiffness No longer required pain medication Able to walk well climb up & down—before had to lift rt leg with hands Increased appetite & strength Gained 10 lbs	Complete disappearance of three fixed stony nodules Two returned after four months	Increased 7 → 11 → 17 (B)	No change 7 → 9 → 8 (B)	Progression	Decreased (6 8 → 1 9 mg /24°)	x	x	4½ months
WC 77	0	11-22-52 50 1 14 53 100	Some decrease in difficulty of urination Nocturia from 7 8X to 3X residual from 300 cc to 90 cc Disappearance of back pain Increased appetite	Shrinking of gland from 3+ to 1+ with loss of nodularity and marked softening After 3 months begin to increase in size	Decreased 7 → 1 (B)	No change 5 → 7 (B)	No change	1 0 No change	x	x	4 months
RB‡ 64	x	2 20-53 50	Marked increase in strength sense of well being appetite Loss of nausea and vomiting	No change	Decreased 22 → 8	Not done	Progression	Decreased (2 4 → 1 8)	x	x	3 months (Still doing well)

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* Referred by Dr Frederick S Howard

† Referred by Dr Miley B Wesson

‡ Referred by Dr Sidney Olsen

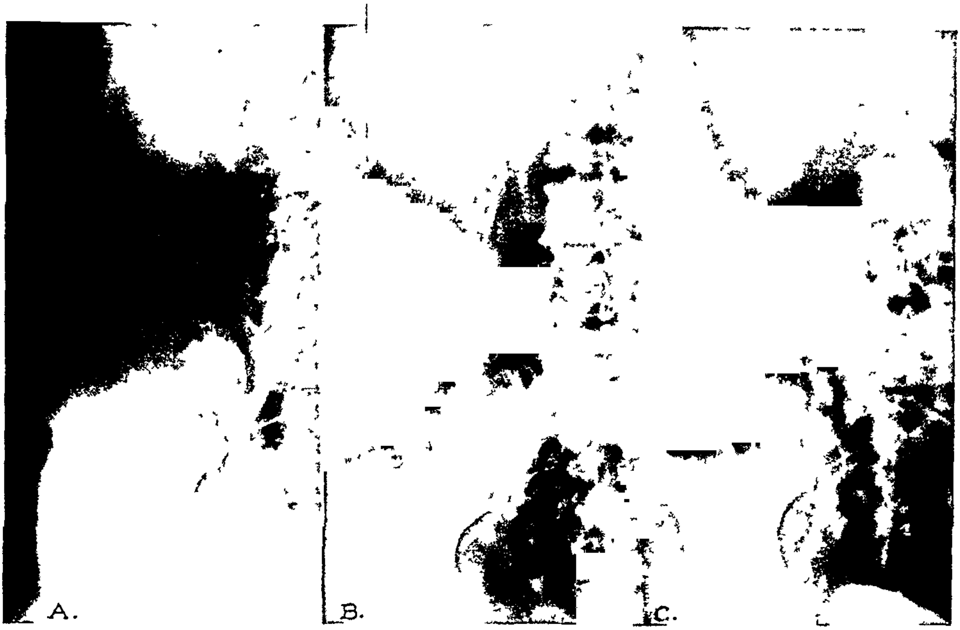

FIG. 1. *A*, excretory urogram showing hydronephrosis, secondary to ureteral involvement by prostatic carcinoma. *B*, after remission on cortisone therapy, showing regression of dilatation *C*, after relapse.

4. 17-Hydroxy-corticoid excretion (compound F). The urinary excretion of compound F was studied in 5 of the patients. The initial levels averaged 13 mg./24 hrs. and all were considered within the normal range. Following the administration of cortisone they all had the expected increase in 17-hydroxycorticoid excretion.

COMPLICATIONS

The only complication from cortisone therapy encountered in our series was the reactivation of an old ulcer in one patient. His symptoms responded to extensive medical therapy despite the continuation of cortisone. No hemorrhage or perforation occurred, although this danger should be kept in mind. Therefore, it would be unwise to treat a patient with a known active or recently active ulcer with cortisone.

All of our patients were placed on a low sodium diet to prevent the possible occurrence of edema from the sodium retention action of cortisone. Those who did not have frank cardiac disease were placed on a diet containing 1 gm./24 hrs. of sodium, and the others on 300 mg./day. The patients on 50 mg. cortisone a day were given 3 gm. of potassium chloride (tablets) by mouth each day. When the cortisone dose was raised to 100 mg./day, the potassium chloride was increased to 6 gm. in divided doses. If stilbestrol should be given along with cortisone, then the dangers of salt retention and subsequent edema would be much increased. Frequent injections of a mercurial diuretic might then be necessary.

No difficulty with hypertension was encountered. One patient was a mild diabetic but no adverse effects were noted.

The dangers of sudden withdrawal of cortisone after a prolonged course are

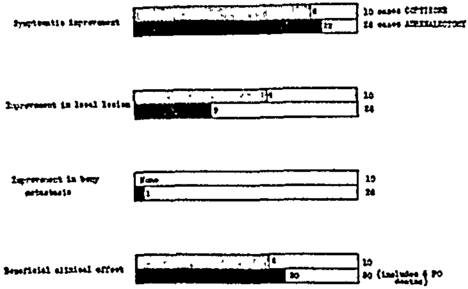

FIG. 2. Cortisone and bilateral adrenalectomy: comparative results (adrenalectomy figures are from the combined series of Huggins and Bergenstal,[3] West et al.[16] Harrison et al.[11] and Leberman et al.[17])

real inasmuch as such patients would be temporarily in a state of adrenal insufficiency. By gradual withdrawal, this complication can be avoided.

THE NUMBER OF PATIENTS OBTAINING REMISSION AND THE LENGTH OF THIS REMISSION

We feel that 8 out of the 10 patients had a clinical remission on cortisone therapy and in 6 out of these 8 there was some evidence of tumor regression by change in the local prostatic lesion or acid phosphatase decrease.

However, the length of the remission was relatively short and varied from 17 to 180 days with an average of 82 days.

COMPARISON WITH PUBLISHED CASES OF BILATERAL ADRENALECTOMY

Since we have attempted by means of large doses of cortisone to produce a "medical adrenalectomy," a comparison of our results with the effects of surgical bilateral adrenalectomy is important. We have drawn on the published results of four series, those of Huggins[3] (University of Chicago), West[16] (Memorial Hospital, New York), Harrison[11] (Peter Bent Brigham Hospital), and Leberman[17] (University of Pennsylvania). Together these give a total of 26 patients available for analysis, omitting 4 additional patients who died in the immediately post-operative period (fig. 2).

1. Symptomatic improvement. Twenty-two out of the 26 patients had symptomatic improvement. Again, here as in our cortisone series, the most striking thing noted was the relief of severe and often crippling bone pain.

2. Improvement in local prostatic lesion. Nine out of the 26 patients were noted to have marked decrease in the size of their local pelvic lesions.

3. Acid and alkaline phosphatase. Six of the 26 patients had a consistent decrease in acid phosphatase following adrenalectomy. Alkaline phosphatase data are difficult to interpret.

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[16] West, C. D., Hollander, V. P., Whitmore, W. F., Jr., Randall, H. T. and Pearson, O. H.: The effect of bilateral adrenalectomy upon neoplastic disease in man. Cancer, 5: 1009–1018, 1952.

[17] Leberman, P.: Bilateral adrenalectomy in prostatic carcinoma. (In press.)

4. Changes in bony metastases by x-ray. As was seen in the cortisone series, 18 out of 20 showed a steady progression of metastases. One patient of Harrison had definite improvement in the metastatic lesions and one in the Memorial Hospital series perhaps had temporary arrest.

5. Number of patients with remission and length of remission. Twenty of the 26 patients surviving bilateral adrenalectomy (omitting 4 additional patients dying postoperatively) were felt to have clinical remissions.

The period of improvement in the Memorial Hospital series varied from 14 to 220 days, averaging 83 days. This is almost identical to the average length of remission in our cortisone series (82 days). However, the average length of remission in the other adrenalectomy series appears to be considerably longer.

EFFECTS OF BILATERAL ADRENALECTOMY AFTER CORTISONE IS NO LONGER EFFECTIVE

We performed late bilateral adrenalectomy on 3 of our 10 patients. Two were operated on after exacerbation occurred following good remission from cortisone alone. One of these (H.M.) had beneficial symptomatic effect from cortisone for two months without improvement in local lesion or metastases. Adrenalectomy was performed 2 months after cortisone was discontinued. At present, 6 months after operation, he is back working hard on his cattle ranch and is asymptomatic, whereas before he was bedridden. His acid phosphatase excretion decreased from a preoperative level of 4 Bodansky units to 1 unit after one month and 2 units after eight months. A large metastatic lesion in the right inguinal region which was extremely tender and painful immediately became no longer painful but only started to decrease in size during the past month, along with marked shrinking of his local prostatic lesion. It may be of some significance that in the last 6 weeks his maintenance dose of cortisone was increased from 37.5 mg. to 75 mg. per day. He has had an excellent clinical remission.

The second patient (F.C.) was completely relieved of his severe pain for four weeks after operation but then began having pain as severe as before. It is now 5 months since operation. He requires 75–100 mg. of cortisone a day to prevent adrenal insufficiency. No improvement is noted in his local lesion and there has been progression of the metastases. His acid phosphatase decreased from 22 Bodansky units to 6 units after four weeks but now is 13 units. No change occurred in alkaline phosphatase excretion.

The third patient (G.W.) was operated upon after a month of cortisone therapy had failed to produce any symptomatic relief or alter his progressive downhill course, although it caused his local lesion to disappear by rectal palpation. Adrenalectomy gave him marked symptomatic improvement which, however, lasted less than eight weeks. During this period, his acid phosphatase excretion which had fallen from 45 King Armstrong units to 26 units on cortisone, rose progressively to 82 units. His alkaline phosphatase, which had risen from 29 units to 96 units, fell progressively to 50 units. He died from his malignant disease eight weeks after surgery.

DISCUSSION

The basis for endocrine therapy in carcinoma of the prostate stems from Huggins' initial work[18, 19, 20] with bilateral orchiectomy and estrogen therapy. From this he postulated that prostatic cancer represents an overgrowth of adult prostatic epithelial cells and like these cells, it undergoes atrophy when the androgens are reduced. Prostatic carcinoma is therefore dependent on the presence of circulating androgen for its growth. Castration or testicular inhibition by decrease of the pituitary gonadotropin output by estrogen results in a decrease in androgen which in turn prodces a decrease in the size of the tumor and in the function of the cancer cells.

After orchiectomy there is a fall in 17-ketosteroid excretion, followed by an increase for prolonged periods [Scott and Vermeulen[21]]. The preliminary fall is due to removal of the gonads. Increased extragonadal production of androgens presumably in the adrenal glands might account for later relapse after orchiectomy. Enlargement of the adrenals has been described in patients no longer responding to anti-androgen therapy. The mechanism for this increased adrenal androgen production for a long time was thought to be by stimulation of the increased pituitary gonadotropin which results from castration. This theory has now been questioned and the exact mechanism is still uncertain.

Huggins feels that cancer of the prostate eventually becomes autonomous, that is independent of androgen, and is no longer repressed by anti-androgenic therapy. Total failure of castration and estrogen therapy in approximately 20 per cent of the patients could then be explained on the basis of primary androgen independence. Support of this theory comes from Deming's work[22] on intraocular tissue transplants in which it was found that after passage through 8 male generations, the tissue then became independent of androgen and was able to grow in an estrogenized animal.

In the last few years, attempts have been made to diminish androgen secretion by the suppression of the pituitary gland by hormones other than estrogens. Trunnell et al.[23] used progesterone in the treatment of patients with advanced prostatic carcinoma on the basis of Albright's theory[24] that androgen production

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[18] Huggins, C. and Hodges, C. V.: Studies on prostatic cancer; the effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Research, 1: 293–297, 1941.

[19] Huggins, C., Stevens, R. E., Jr. and Hodges, C. V.: Studies on prostatic cancer; the effects of castration on advanced carcinoma of the prostate gland. Arch. Surg., 43: 209–223, 1941.

[20] Huggins, C., Scott, W. W. and Hodges, C. V.: Studies on prostatic cancer; the effects of fever, of desoxycorticosterone, and of estrogen on clinical patients with metastatic carcinoma of the prostate. J. Urol., 46: 997–1006, 1941.

[21] Scott, W. W. and Vermeulen, C.: Studies on prostatic cancer; excretion of 17-ketosteroids, estrogens and gonadotropins before and after castration. J. Clin. Endocrinol., 2: 450–456, 1942.

[22] Deming, C. L. and [illegible] hormonal factor in heterologous growths of human [illegible] 948.

[23] Tr[illegible] V., Whitmore, W. F. and Woodard, H. G.: The use of progesterone in treatment of cancer of the prostate. J. Clin. Endocrin., 11: 663–676, 1951.

[24] Albright, F. and Elrick, H.: An attempt to classify hormonal disorders of the hypophysis. Tr. A. Am. Physicians, 61: 42–53, 1948.

depended on the secretion of luteinizing hormone (LH). They had excellent results in 8 of 10 patients that had had no previous therapy and in 3 of 6 patients who were in relapse after the usual hormonal therapy. However, some doubt has been cast on the LH theory as the major mechanism, since 17-ketosteroids increase after ACTH administration. As has been shown, the 17-ketosteroid excretion will decrease with inhibition of ACTH by cortisone.

Although the evidence for the importance of androgens in cancer of the prostate is sound, it does not extend to their exact role in the induction of the cancer or in the maintenance of its growth. Questions arise because of the well established fact that the average testis produces less androgen and more estrogen as age advances and yet cancer of the prostate is principally a disease of the elderly male. Moreover, studies on average 17-ketosteroid levels in these patients as compared with other males in the same age group showed no essential difference. The possibility thus occurred to us that there might be basic metabolic differences in these patients so that their androgens were not primarily secreted as 17-ketosteroids which would explain the dilemma. However, our few experiments[25] with exogenous androgen would indicate that this hypothesis was wrong since 2 untreated patients with prostatic carcinoma had the same rise in urinary 17-ketosteroids after a test dose of 100 mgm. of testosterone propionate as a young and an old normal patient. However, they don't completely rule out the possibility of abnormal metabolism of endogenous, as opposed to exogenous, androgen. Brendler and Scott[26] used large doses of testosterone on 3 patients with advanced disease. Two showed general improvement for a while, similar to the patients treated by cortisone or adrenalectomy and yet their acid phosphatases rose and the disease progressed—a non-specific effect of the steroid similar to that we have seen with cortisone.

Bilateral adrenalectomy was undertaken by Huggins because of experimental evidence on the role of the adrenals in neoplasia[27, 28] and in cancer of the prostate in particular, to remove the extra-gonadal source of androgen. This surgery has been successful only in carcinoma of the breast and carcinoma of the prostate, both of which are tumors felt to be under some endocrine control.

That the use of rather large suppressive doses of cortisone alone (in advanced carcinoma of the prostate) gives results similar to surgical bilateral adrenalectomy is not surprising when one considers that essentially what we have done is to produce a "medical adrenalectomy." This is analogous to the use of estrogen alone in place of orchiectomy. Most of the symptomatic improvement seen in our patients on cortisone can be explained on the basis of the nonspecific effect of the drug and most of these effects can be seen in other diseases treated with cortisone. Because of this, one of our colleagues has aptly called cortisone the

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[25] Miller, G. M.: (Unpublished data.)

[26] Brendler, H., Chase, W. E. and Scott, W. W.: Prostatic cancer; further investigation of hormonal relationships. Arch. Surg., 61: 433–440, 1950.

[27] Ingle, D. J. and Baker, B. L.: The effect of adrenalectomy in the rat upon the rate of growth of transplantable tumors. Endocrinology, 48: 313–315, 1951.

[28] Funk, C. Tomashefsky, P., Soukup, R. and Ehrlich, A.: The effect of hormonal factors and the removal of certain organs upon the growth of a transplanted rat tumor. Brit. J. Cancer, 5: 280–287, 1951.

"magnificent aspirin." However, this is essentially the same symptomatic improvement as seen in patients after adrenalectomy, who of course are maintained on cortisone.

A point of confusion and a cause for speculation is the apparent improvement in the local prostatic lesion in a fair number of our own patients, and in the adrenalectomy patients as well, accompanied by occasional improvement in acid phosphatase, and yet with progression of bony metastases in most of the patients. One possible explanation is that the local lesion may be less undifferentiated and thus more susceptible to hormonal influence than the metastases.

Other mechanisms can only be mentioned here. From our findings and others[29] on the decreased thyroid function with cortisone administration, the possibility that the resulting decrease in general metabolism will also affect the metabolism of the tumor cells also exists but this does not explain the difference between the local lesion and the metastases. The question of inhibition of thyrotropic hormone as well as ACTH by cortisone arises.[30] Still another explanation of the shrinking of the prostate with cortisone arises from the known inhibiting effect of the drug on inflammatory tissue and thus the apparent shrinking of the tumor may be merely a decrease in the fibrous stroma. It must be considered that in cases no longer responding to one type of hormonal treatment, the residual tumor cells may have adapted themselves to become dependent on the new environment created by the treatment. This could explain the return of the local lesion in our two patients under these circumstances. However, Nathanson[31] contends the tumor may have acquired vulnerability to effective therapy with other hormones. Hence, it appears that a shift in the endocrine status, as by cortisone, of the host may affect the response of a given tumor to hormonal agents. Somehow not now apparent cortisone changes the cellular environment or intrinsic cellular processes, but in a way which is peculiar to each neoplasm or group of neoplasms.[32]

SUMMARY

Ten patients with disseminated carcinoma of the prostate in severe exacerbation following previous remission from orchiectomy and estrogen therapy were treated with cortisone, starting with 50 mg. per day by mouth in divided doses. Eight out of the 10 patients had marked subjective improvement and 6 out of the 10 had objective improvement with decrease in the size of the local lesion and in 2, decrease in acid phosphatase. These results are comparable to those reported after bilateral adrenalectomy. The duration of beneficial response was rather short, averaging 82 days. This is probably shorter than after surgical adrenalectomy. Hormonal studies were done and their significance to our knowledge of hormonal interrelationships in carcinoma of the prostate is discussed.

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[29] Halmi, N. S. and Barker, S. B.: Histo-physiological effects of cortisone on rat pituitary and thyroid. Endocrinology, 51: 127–134, 1952.

[30] Fredrickson, D. S., Forsham, P. H. and Thorn, G. W.: The effect of massive cortisone therapy on measurements of thyroid function. J. Clin. Endocrinol. and Metab., 12: 541–553, 1952.

[31] [illegible]

CONCLUSIONS

When orchiectomy and estrogen therapy have failed in patients with advanced prostatic carcinoma, cortisone treatment will often give an additional remission.

Adrenal suppression by cortisone gives clinical effects similar to bilateral adrenalectomy in these patients. With either treatment, the effects are temporary but are of somewhat shorter duration with cortisone alone.

Bilateral adrenalectomy after cortisone has become ineffective still gives additional relief to the patients.

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TACE IN PROSTATIC CANCER: CLINICAL AND BIOCHEMICAL CONSIDERATIONS

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Tremendous strides have been made in the treatment of prostatic cancer since Huggins[1] developed the concept that androgen was capable of activating tumor growth in this condition, and that inhibiton of androgen production or action by orchiectomy or estrogen administration often resulted in reduced activity of the neoplasm.[1, 2] The initial improvement which resulted from orchiectomy and estrogen administration in many cases has been followed by exacerbation of the tumor, and this occurrence has led Huggins[3] to suggest that androgen from an extragonadal source, the adrenal, was responsible.

It is well known that the administration of estrogens results in inhibition of the pituitary gonadotrophins so that the production of testicular androgens is markedly diminished.[4, 5] A further result of estrogen administration may be the neutralization of testicular and adrenal androgen before or at the prostatic tissue.[6] Recent evidence,[7] however, indicates that these beneficial effects of estrogen may be minimized due to the fact that estrogens themselves may be responsible for increased corticotrophin production. Whether the administration of estrogen actually results in increased adrenal androgen production is not known with certainty, but Harrison[8] considers this a distinct possibility, especially where excessively large doses of estrogen are used.

TACE,* a new synthetic estrogen, differs from other synthetic and natural estrogens in that it produces little or not adrenal hyperplasia in female rats[9] or in male rats.[10] A further difference is evidenced by the fact that in laboratory animals its administration does not produce pituitary enlargement.[9, 11]

On the basis of these differences and in view of the probability that TACE would not cause adrenal stimulation in man, we have administered it during the past 32 months to a series of 42 patients suffering from prostatic cancer. These patients were between the ages of 50 and 90, and the disease presented wide variations. Five patients had demonstrable metastases on admission, but the

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Read at annual meeting, South Central Section of American Urological Association, Kansas City, Mo. September 21–23, 1953.

[1] Huggins, C. an Hoddges, C. V.: Cancer Res., 1: 293–297, 1941.

[2] Herbst, W. P.: J.A.M.A. 120: 1116–1120, 1942; Urol. & Cutan. Rev., 46: 691–694, 1942.

[3] Huggins, C. and Scott, W. W.: Ann. Surg., 122: 1031–1041, 1946.

[4] Heckel, N. J.: Clinics, 5: 860–877, 1946.

[5] Moore, C. R. and Price, D.: Am. J. Anat., 50: 13–72, 1932.

[6] Huggins, C. and Clark, P. J.: J. Exp. Med., 72: 747–762, 1940.

[7] Tepperman, J. and Tepperman, H. M.: Ann. Rev. Physiol., 12: 503, 1950.

[8] Harrison, J. H. and Poutasse, E. F.: Am. J. Med., 11: 55–66, 1951.

* TACE is the trade-mark of the Wm. S. Merrell Company, Cincinnati, Ohio, for its brand of chlorotrianisene (tri-p-anisylchloroethylene).

[9] Thompson, C. R. and Werner, H. W.: Proc. Soc. Exper. Biol. and Med., 77: 494–497, 1951.

[10] Trunnell, J. B.: Effect of TACE in the male rat. Read at TACE symposium, Cincinnati, Ohio, January 17, 1952.

[11] Shipley, E. G. and Meyer, R. K.: Some biological effects of TACE in animals. Ibid.

acid phosphatase was elevated in 9. Alkaline phosphatase was above normal in only 2 patients. Five patients had occult carcinoma. Twenty of the patients have had orchiectomy.

Estrogenic treatment was begun immediately following the diagnosis. Twenty-eight patients have received only TACE and the others who had received other estrogens previously were given TACE when it first became available. The usual dose of TACE was 24 mg. per day, but in some instances as much as 180 mg. were given daily. Nine of the patients were given TACE for 2½ years, 10 patients for 2 years, 6 patients for 1½ years, and 4 patients for slightly more than one year.

Twenty-nine patients in this series are still living and show definite improvement and a general well-being with normal phosphatase values and are free from metastatic lesions.

The following are instances of marked improvement when TACE was substituted for other estrogens:

Mr. J. R. M. had a transurethral resection in December 1948 and received 5.0 mg. of stilbestrol daily by mouth and 5.0 mg. weekly intramuscularly. Metastatic lesions of the lumbar spine and pelvis became progressively worse. TACE was begun in April 1951 and his condition improved remarkably. There was an increase in weight, his appetite improved, the blood phosphatase became normal, and the metastatic lesions disappeared. The improvement continued for 8 months, but the prostatic disease recurred and the patient died 6 months later.

Mr. H. A., aged 59, underwent transurethral resection for adenocarcinoma with metastases in April 1949. He received ethinylestradiol until December 1950 at which time he began to lose weight and suffered from pain radiating down the legs. Pelvic metastases were evident and the acid phosphatase was slightly elevated. Ethinylestradiol was discontinued and TACE was administered in a daily dose of 24 mg. At the present time, nearly 3 years after TACE therapy was begun, the patient is in excellent health with no local regrowth of tissue and no evidence of metastatic lesions.

Thirteen patients have succumbed during the study: Five of the deaths were attributed to cardiac disease. Nine of these patients had received other estrogens before TACE was administered and 4 had had only TACE. Seven of these 13 patients had survived for four or more years. At autopsy, the adrenal gland was normal microscopically and macroscopically in five patients who had received TACE for varying periods just before their death.

The estrogenic substances other than TACE caused nausea in 6 patients, vomiting in 3 patients, edema of the extremities in 3 patients, and some tenderness of the breasts in all cases. It is interesting to note that after discontinuing the other estrogens because of these side-effects, TACE was given and all symptoms disappeared. No patient has ever had sufficient gastro-intestinal upset, edema, or mastalgia while taking TACE to warrant its withdrawal.

In view of the important role which androgens play in prostatic cancer, 17-ketosteroid determinations were carried out on a number of patients. Human urine contains steroids which have ketone oxygen at C.17. Some of these steroids

TABLE 1. *Ketosteroid levels in normal men*

AGE GROUP	KETOSTEROID EXCRETION, MG./24 HOURS	REFERENCE
20–40	8–25	12
50–52	11.3	13
50–75	9.0	15
50–59	6.0	14
60–69	4.8	14
62–76	5.0	13
70–75	2.9	14
71–75	3.2–3.5	12

are phenolic while others are neutral. These latter are commonly called "17-ketosteroids." The principal members of this group are androsterone, etiocholanone, isoandrosterone and dihydroisoandrosterone. The first two of these arise in part from the testes, while all represent excretion products of some of the steroids of the adrenal cortex. Accordingly, the measurement of the 17-ketosteroid output provides a rough biochemical index of testicular and adrenocortical activity.

While the total neutral 17-ketosteroids levels in normal men between 20 and 40 years of age fall within the limits of 8 mg. to 25 mg. per twenty-four hours, the levels for older men are much lower.[12] In 5 normal men between the ages of 71 and 75 years, values of 3.2 mg. to 3.5 mg. were reported.[12] In 6 normal men whose ages ranged from 62 to 76, Frame and Jewett[13] found that the mean total 17-ketosteroid level was 5.0 mg. per 24 hours, while that for normal men between 50 and 52 was 11.3 mg. Hamilton and Hamilton[14] studied the effect of aging on ketosteroid excretion and found that in the age groups of 50 to 59, 60 to 69, and 70 to 75, the total ketosteroids excreted in 24 hours were 6.0 mg., 4.8 mg., and 2.9 mg., respectively. Kenigsberg[15] carried out 60 determinations on 18 normal men between the ages of 50 and 75 years, and found the group average to be 9.0 mg. per 24 hours with a range of 5 mg. to 15 mg.

In untreated prostatic cancer in men between 53 and 54, it was found that the total 17-ketosteroid excretion per 24 hours was 8.9 mg.[13] In an older age group, 62 to 76, the average value was 5.0 mg. with a range of 3.3 mg. to 6.8 mg. Scott and Vermeulen[16] found the precastration level in 10 men (47 to 80) with prostatic cancer to be 7.6 with a range of 3.6 to 11.7, while Satterthwaite, Hill and Packard[17] found the average value to be 5.2 mg. in a group of 14 patients with carcinoma of the prostate whose ages ranged from 54 to 83 years. The results of these investigations are summarized in tables 1 and 2.

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[12] Conference on ketosteroids, Josiah Macy Fund, 1942.

[13] Frame, E. G. and Jewett, H. J.: J. Urol., 52: 330, 1944.

[14] Hamilton, H. B. and Hamilton, J. B.: Aging in apparently normal men. I. Urinary titres of ketosteroids and of alpha-hydroxy and beta-hydroxy ketosteroids. J. Clin. Endocrin., 8: 433, 1948.

[15] Kenigsberg, Samuel, Pearson, Sidney and McGavack, T. H.: J. Clin. Endocrin., 9: 426, 1949.

[16] Scott, W. W. and Vermeulen, Cornelius: J. Clin. Endocrin., 2: 450, 1942.

[17] Satterthwaite, R. W., Hill, J. H. and Packard, E. F.: J. Urol., 46: 1149, 1941.

TABLE 2. *Ketosteroid levels in untreated prostatic carcinoma*

AGE GROUP	KETOSTEROID EXCRETION, MG./24 HOURS	REFERENCE
53–54	8.9	13
47–80	7.6	16
54–83	5.2	17
62–76	5.0	13

In view of the wide range that exists in the ketosteroid levels of young men, it is not surprising to find a similar variation in the aging male with and without prostatic cancer. While differences exist between the ketosteroid levels in the control groups and those with prostatic cancer it can be stated that no significant difference has been demonstrated. It is also apparent that there is fairly close agreement between the results of different investigators.

Following castration for prostatic cancer, Scott and Vermeulen[16] found that the average precastration levels of 7.6 dropped to a figure of 3.4 in an average period of 15.8 days following castration. There then followed a gradual rise to an average figure of 13.9 in an average period of 101 days and this figure then fell to 11.4 mg. at the end of an average period of 142 days. A similar study on an additional ten patients for a longer period showed that after an average period of thirteen months following castration, the ketosteroid level had dropped to 6.6 mg. per 24 hours, a figure not significantly different from those seen in the control group and in untreated cases of prostatic cancer.

Since considerable clinical improvement usually follows castration, much doubt is thus cast upon the validity of the widely held belief that low 17-ketosteroid levels must necessarily be present before clinical improvement is noted. This does not mean that androgens do not play an important part in the causation of prostatic cancer, as Huggins has claimed, but the results suggest that there may be no correlation between 17-ketosteroids determined chemically and androgens determined biologically. While it has been shown that there is a close agreement in some conditions between 17-ketosteroids and androgens,[18] these authors indicate that in liver disease and gynecomastia, the ratio of androgen to 17-ketosteroids is low. Not all 17-ketosteroids possess the same degree of androgenicity and it should be borne in mind that the terms, "androgen," and "17-ketosteroids," are not necessarily synonymous.[3] If high 17-ketosteroid levels, per se, were responsible for prostatic cancer, it is difficult to reconcile this with the fact that prostatic cancer is extremely uncommon in the younger age group in which 17-ketosteroid levels are characteristically high, and most common in the older group whose levels have been found to be low. We have not carried out determinations which would indicate a relationship between 17-ketosteroids and biological androgens in prostatic cancer, but it would seem that such a study would produce extremely valuable information.

In the present study, the total neutral 17-ketosteroid determinations were carried out on the urine of 19 patients who were suffering from prostatic cancer. All but 1 of these patients had received varying amounts of TACE prior to the

[18] Zarrow, M. X., Munson, P. L. and Salter, W. T.: J. Clin. Endocrin., 10: 692, 1950.

TABLE 3. *Observations in 15 patients with prostatic carcinoma receiving* TACE (no orchiectomy)

	AGE	TACE STARTED	DAILY DOSE, 12 MG. CAPSULES	TOTAL CAPSULES	DAYS ON TACE	DATE OF K. S.	KETOSTEROIDS, MG./24 HRS.	ACID PHOSPHATASE	PRESENT STATUS	METASTASES
J. H.	60	1/ 3/51	2	654	327	11/26/51	11.0	5/50 .4 7/50 .3 2/51 .4	Good	none
H. N.	65	10/19/51	2	58	49	11/29/51	18.5	3.8	Good	none
F. T.	70	11/26/51	4	76	19	12/14/51	5.7	.02	Good	none
H. H.	55	1/13/51	2	664	317	11/26/51	21.6	11/51 2.8 11/52 2.7	Died 12/52	none
H. A.	60	12/26/50	2	678	340	12/ 4/51	16.5	12/50 1.6	Good	none
					373	1/ 7/52	26.5	12/51 3.2		
				1880	910	7/24/53	14.0			
J. R.	85	9/ 6/51	2	190	95	12/11/51	3.6	9/51 2.0 1/52 2.4	Died 8/52	none
J. J.	70	11/51	2	78	39	12/13/51	5.5	10/51 15.4 11/51 12.0 2/52 0.4	Died 4/53	none
F. P.	65	4/24/51	3	729	240	12/24/51	4.7	11/50 32.0 12/50 7.2 12/51 5.0	Fair	Yes
G. B.	63	7/ 1/51	3	513	171	12/21/51	9.8	7/51 .4 12/51 .3 3/52 .5 6/52 .1	Fair	none
J. J.	90	9/26/51	2	100	90	12/24/51	9.2	3.6	Good	none
						1/ 3/52	6.6			
E. P.	62	4/24/51	2-4	466	240	12/17/51	8.6	9/50 2.0 12/51 3.0	Good	none
J. R.	64	10/ 3/51	4	288	72	12/14/51	11.1	9/51 .4 12/51 .1	Good	none
C. S.	85	1/15/51	2	660	360	12/15/51	9.0	1/51 3.8 1/52 2.2	Good	none
J. M.	75	4/18/51	2	615	240	12/ 7/51	14.1	12/48 2.9 12/51 2.9	Died 8/52	yes
E. M.	70	1/ 6/51	2	720	365	1/52	6.8	1/52 1.8	Good	none

TABLE 4. *Observations in 3 orchiectomized patients with prostatic carcinoma receiving* TACE

	AGE	TACE STARTED	DAILY DOSE, 12 MG. CAPSULES	TOTAL NO. CAPS.	DAYS ON TACE	DATE OF ORCHIECTOMY	DATE OF K. S.	KETOSTEROIDS, MG./24 HRS.	ACID PHOSPHATASE	PRESENT STATUS	METASTASES
C. N.	70	1/ 1/51	2	626	270	10/51	11/26/51 1/ 4/52	5.9 17.7	9/49 1.8 11/51 3.4 1/52 4.6	Died 1/52	none
W. F.	57	7/15/51	2	270	150	7/51	12/ 3/51	7.0	12/51 2	Good	none
F. M.	80	8/13/51	2–15	1383	180	11/42	12/12/51 2/ 5/52	5.5 9.8	12/51 190 1/52 356	Died 2/52	yes

TABLE 5. *Observations in patients not suffering from cancer of the prostate*

	AGE	DATE OF KETOSTEROID DETERMINATIONS	KETOSTEROIDS, MG./24 HRS.
F. T.	70	11/26/51	14.8
A. S.	70	12/17/51	8.3

collection of the urine specimen. Orchiectomy had been performed on 3 patients before the ketosteroid determinations were done and after the determination in 1 case. Ketosteroid determinations were also carried out on the urine of 2 patients in a similar age group who did not have prostatic cancer. The method of Hawk[19] was used with slight modifications to make for accuracy with the spectrophotometer and a solution of dihydroandrosterone was used as a standard. The results are given in tables 3, 4, and 5.

In the 15 patients on whom orchiectomy had not been performed and who were receiving only TACE, the range of 17-ketosteroid excretion was 3.6 mg. to 26.5 mg. with an average of 11.3 mg./24 hours. This latter value is in close agreement with the findings of O'Conor and Sokol.[20]

The average value of the determinations in a group of patients who were orchiectomized and who have received TACE was 9.2 mg. This figure was not significantly different from that found in the preceding group (11.3 mg.) and also not significantly different from Scott's figure of 6.6 mg.

In our two control patients who do not have cancer and who received no TACE, the mean value was 11.5 mg., while one determination in a case of untreated prostatic cancer was 8.5 mg.

A relationship between high 17-ketosteroids and the clinical condition was not established in our study, but it must be stated that a sufficient number of determinations was not done to arrive at any conclusion other than to say that a wide variation in levels existed. Insofar as establishing a relationship between the clinical condition and 17-ketosteroid levels is concerned, it would be extremely difficult to establish this while the patient is receiving an estrogen because the factor of biological antagonism between estrogens and androgens must be considered. Our findings also indicate that there was no relationship between 17-ketosteroid levels and acid phosphatase determinations. The excretion of 17-ketosteroids appeared to be unaffected by the administration of TACE.

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[19] Hawk, P. B., Oser, B. L. and Summerson, W. H.: Practical Physiological Chemistry. Philadelphia: The Blakiston Co., 1948, p. 700, 12th ed.

[20] O'Conor, V. J. and Sokol, J. K.: Evaluation of TACE as a therapeutic agent in prostatic carcinoma. Read at TACE Symposium, Cincinnati, Ohio, January 17, 1952.

SUMMARY AND CONCLUSIONS

A series of 42 patients suffering from prostatic cancer has been treated by surgical methods and the new synthetic estrogen, TACE, during a period of 32 months.

TACE was well tolerated even when extremely large doses were administered and there was a virtual absence of undesirable side-effects.

In many patients in whom the disease had become resistant to other synthetic and natural estrogens the administration of TACE resulted in clinical improvement. This was characterized by an increase in weight, a decrease in pain, an improvement in the blood picture, and regression of metastatic lesions.

In five TACE-treated patients who came to autopsy there was no evidence of the adrenal hyperplasia which has been observed in laboratory animals following the administration of some other synthetic estrogens.

Sufficient time has not yet elapsed for us to compare the survival time in TACE-treated patients to that observed in patients treated with other synthetic or natural estrogens.

The urinary excretion of 17-ketosteroids was investigated in 21 patients who had received daily doses of 24 mg. to 180 mg. of TACE for many months and the findings indicate that the administration of TACE has no adverse effect upon adrenocortical function. The significance of 17-ketosteroids determinations in prostatic cancer is discussed.

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RESULTS OBTAINED BY ENDOCRINE CONTROL THERAPY FOLLOWED BY RADICAL PERINEAL PROSTATECTOMY IN TWENTY-FIVE SELECTED CASES OF ADVANCED CARCINOMA OF PROSTATE

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It was to be expected that the marked regression of the carcinomatous prostate which so frequently resulted from endocrine control therapy would suggest to a number of observers a broadened field of usefulness for the perineal prostatectomy in the treatment of selected cases of advanced carcinoma of the prostate. Vallett in 1944 seems to have been the first to use this combined therapy on a case of this sort but unfortunately the patient died too soon after surgery to permit any conclusions as to its efficacy. Later in the same year Parlow and then Colston recommended its use in selected cases. In December of that year Scott and Benjamin reported 2 cases which had recently been treated in this manner. In 1947, Colston and Brendler reported one death within a year in 7 cases that had been followed 2 years after surgery. Parlow and Scott in 1949 reported their results in a series of 14 cases treated by this combined therapy. One year later Scott and Parlow reported that 22 cases had been treated by this method in their clinic and presented a detailed report on the first 13 cases, all of which were living and apparently well after the institution of therapy. Scott in 1953 presented a detailed report on 21 selected cases of advanced carcinoma of the prostate that had been treated by this method and which had been followed three years or more after treatment was started.

Inasmuch as any attempt to evaluate the efficacy of this combined therapy in the treatment of selected cases of advanced carcinoma of the prostate gland is necessarily influenced by the types of case included in such a study, it might be helpful if our determining selective factors were presented and discussed at this time. Obviously those patients, in whom, because of recent origin or latency of growth, the carcinoma, when first discovered, is so situated as to permit a reasonable chance for its complete removal by radical surgery, should not be included in this group. All patients with proven metastases when first seen, regardless of their response to hormone therapy, are not suitable candidates for the follow-up radical surgery. Radical surgery offers practically no hope of cure to the patients without metastases in whom the local growth is a little too extensive to permit its complete removal when first seen and who fail to respond to endocrine therapy. Where the local growth has advanced to such an extent as to result in the formation of a well-defined, intervesicular plateau when the patient is first seen, it is reasonable to assume that lymphatic and perineural extension beyond the palpable area may have occurred even though the presence of metastases cannot be proven. In such cases, regardless of a remarkable local response, it would seem that while a follow-up radical perineal prostatectomy

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might increase the patient's life expectancy and freedom from distressing urinary symptoms, it should still be considered of questionable value. In the presence of nodular intravesical extension beyond the bladder neck when the patient is first seen, the combined therapy seems to be contra-indicated. However when the aforementioned conditions have been excluded there still remains a very encouraging number of cases with carcinoma of the prostate from which the patients to be treated by the combined therapy can be selected.

These are the patients in the group of advanced carcinoma of the prostate without metastasis in whom the carcinomatous extension beyond the confines of the prostate, while not marked, is too great to permit its complete extirpation by radical surgery when the patient is examined. It is for the patients in this group, providing their response to hormone therapy has been such that a digital examination at the time of maximum regression suggests that complete extirpation of the carcinomatous lesion might be possible, that we believe a follow-up radical perineal prostatectomy offers a chance for a cure, or failing in this will at least prolong the patient's life and freedom from distressing symptoms. But even some of these patients have to be excluded because advanced age or their general physical condition seem to contra-indicate radical surgery.

It seems to us that the decision as to whether or not the patient is a suitable candidate for radical surgery is less difficult to make on the basis of his age than from the standpoint of his general physical condition. Because of their limited life expectancy and because carcinoma of the prostate is often a very slow process in patients who are 80 or more years of age, we have not used the combined therapy in any instance where the patient was that old when first seen. We have learned that as a result of careful preoperative and postoperative care, proper supportive measures during operation and the availability of very satisfactory antibiotics, the radical perineal prostatectomy, while sometimes requiring a little longer to perform, is seldom more disturbing to the patient than some of the more commonly used surgical procedures upon the prostate. At least three of our patients had a history of coronary disease with cardiographic evidence of damage and yet were no more disturbed by the operation than the average case. As a rule the operative risk due to the presence of general physical disability is little if any greater than that of the other open operations upon the prostate for the correction of prostatic obstruction.

Up to the present time in the urological clinic of the Strong Memorial Hospital, we have treated 31 patients by this combined therapy, 25 of whom have been followed 36 months or more since treatment was instituted. The remaining 6 patients have not been under treatment long enough to warrant an attempt to evaluate the efficacy of the therapy upon them.

Since 21 of the 25 cases that have been followed 3 years or more have been presented in detail in a very recent publication, it might be more profitable at this time to present and discuss in detail the 5 cases in our series in which death was due to local recurrence or metastasis. In all the patients treated by this method the clinical, serological and radiographic studies were negative for the presence of metastasis. Furthermore all blood studies and renal function tests were within normal limits at the time of operation.

CASE REPORTS

Case 1. C. D., S.M.H., 211137, aged 72 when first examined on November 1, 1943, gave a history of gradual diminution in size and force of his urinary stream, increasing frequency and terminal dribbling of 6 months' duration. There had been no loss of weight.

The findings on physical examination were normal for a man his age except for the prostate which was moderately enlarged in all dimensions; its median furrow and notch were shallow and its surface was moderately smooth but very hard. It was fixed in position and extension beyond the base to the region of the seminal vesicles for a short distance had occurred on each side (fig. 1, *A*). His residual urine was 15 cc and a punch biopsy study revealed adenocarcinoma of the prostate.

Following a bilateral orchiectomy, performed on November 22, 1943, regression which was slow and not marked except in the anteroposterior diameter of the gland, reached its maximum point on November 14, 1944 when a follow-up radical perineal prostatectomy was performed. At that time there still remained some induration extending for a short distance towards the seminal vesicle in each side (fig. 1, *B*).

Studies of sections from the surgical specimen showed a scattered collection of large epithelial cells with hyperchromic nuclei and abundant pale-staining cytoplasm. Some of the cells were arranged in acinar fashion, but for the most part, they appeared as solid cords invading the dense connective tissue and smooth muscle. Cancer cells were found in the fascial tissue surrounding the seminal vesicles. Sections of nerves showed tumor cells within their sheaths.

The patient's convalescence was satisfactory and when he was discharged from the hospital 23 days after operation he was voiding satisfactorily and his control was perfect.

Because of his poor response to bilateral orchiectomy the patient was not placed on our routine postoperative course of estrogen therapy until a recurrent nodule was discovered on rectal examination 56 months after prostatectomy (fig. 1, *C*). He was immediately started on stilbestrol therapy which was later supplemented by deep x-ray and local radium treatments. He died of carcinomatosis on May 26, 1950.

This case failed, in at least one respect, to meet our criteria for treatment by this combined therapy. The growth, which was well beyond the confines of the prostate in the region of the seminal vesicles when the patient was first seen,

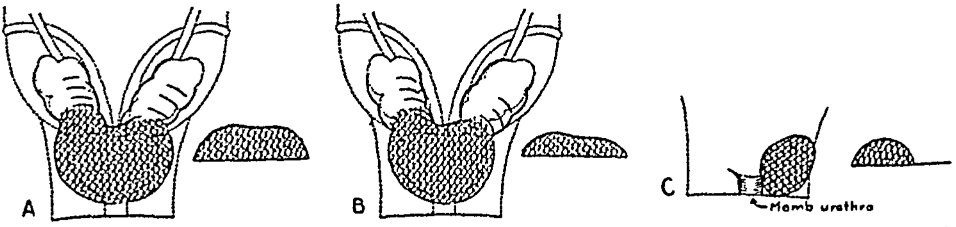

FIG. 1. *A*, prostate before castration November 11, 1943. *B*, only slight regression evident at time of radical perineal prostatectomy November 11, 1944. *C*, location and size of recurrence when first discovered on June 6, 1949.

responded but slightly to control therapy and therefore it is doubtful if a reasonable chance for its complete extirpation was present at the time of radical surgery. Inasmuch as during most of the 82 months that the patient lived following the institution of therapy he was quite comfortable and without urinary symptoms, it would seem that he derived some benefit from the treatment. We believe that we are now able to evaluate the surgical possibilities in cases of this sort much more accurately than at the time this patient was treated.

Case 2. O. J., S.M.H., 237491, aged 61 when first seen on September 17, 1943 complained of gradually increasing frequency, dysuria and dribbling of 3 years' duration.

He appeared to be in good physical condition but on rectal examination a prostate that was very hard and enlarged in all dimensions was found. There was extension of third degree induration beyond the base to the region of both seminal vesicles with beginning intervesicular plateau formation (fig. 2, *A*).

Stilbestrol therapy, 5 mg. a day, gave considerable relief of urinary symptoms but regression was slow so a bilateral orchiectomy was performed on April 5, 1945 and the estrogen therapy was continued. Within 4 months the involved area had regressed and softened markedly. It was firm but movable in spite of definite adhesions along its lateral margins (fig. 2,*B*). The radical perineal prostatectomy was performed on September 9, 1945.

On examination of the gross specimen an area of nodular hardness was found in the region of one seminal vesicle but there was no note that sections were taken from it. The tumor was of a diffuse infiltrating type. In some areas the connective tissue was studded with small acini, nests and cords of tumor cells. Many of the nests contained only 2–3 cells. Studies of sections from the periphery of the surgical specimen in a few instances showed cells in acinar form invading the nerve trunks.

The patient's convalescence was uneventful except that he had almost complete incontinence for a period of 2 weeks following the removal of his catheter. When discharged 28 days after operation his control was better but not perfect.

The patient was followed at regular intervals by the operator until June 10, 1947. At this time there was no evidence of local recurrence and urinary incontinence was only present on occasions of extreme physical fatique. Shortly afterwards he moved from Rochester leaving no forwarding address. A report to us that he was examined elsewhere on January 2, 1952 and found to be well was evidently unfounded. On April 27, 1953 we finally contacted his wife who in-

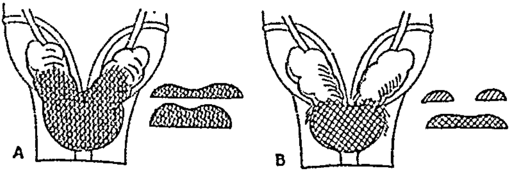

Fig. 2. *A*, prostate before stilbestrol therapy July 2, 1943. *B*, condition after supplementary orchiectomy July 17, 1945 and before radical prostatectomy September 9, 1945.

formed us that he died in Seattle of carcinomatosis on August 26, 1948 probably from a primary lesion of the prostate.

This case differed from the previous one in that the extension of the cancer to the region of the seminal vesicles was considerably greater and the regression due to control therapy was faster and more pronounced. The decision to perform a follow-up radical perineal prostatectomy in spite of very definite extension to the seminal vesicles with intervesicular plateau formation was greatly influenced by the marked response to control therapy. By so doing a criterion for the selection of patients for the combined therapy was violated. Although the patient was not cured the fact that he was quite comfortable during most of the 62 months he survived after treatment was started, suggests that he derived considerable benefit from it.

Case 3. B. F. C., S.M.H., 278670, aged 64 when first seen on April 14, 1948 complained of hesitancy, nocturia, recurrent hematuria and dysuria although a suprapubic prostatectomy had been performed elsewhere 3 years previously. His prostate was at least twice normal in size and the median furrow and notch were shallow. The lateral lobes were smooth but firm, being of second degree induration except at their bases where third degree induration was present, especially on the left side (fig. 3, *A*). As a result of this examination the clinical impression was benign prostatic hypertrophy plus inflammatory reaction. However on cystoscopic examination an irregular, bleeding, suspicious area was seen in the bladder just inside the vesical neck at about 4 o'clock. A diagnosis of adenocarcinoma probably of prostate was made from sections of this area. Treatment was complicated by the presence of moderately severe diabetes.

A bilateral orchiectomy performed on June 12, 1948 was supplemented by estinyl therapy, 0.05 mg. three times a day. By March 11, 1949 the right lobe of prostate had softened and regressed almost to normal size. Although the left lobe had decreased considerably in size, there remained a nodule of third degree induration covering a small area in the region of the base of the seminal vesicle (fig. 3, *B*). Since all studies were negative for metastases and on cystoscopic examination the area in the bladder had disappeared, a radical perineal prostatectomy was performed on March 15, 1949. A liberal cuff of the vesical neck was removed with the prostate and seminal vesicles. Pathological studies from prostate revealed carcinoma showing marked estrogen effect. The patient had good urinary control when discharged on estinyl therapy on April 4, 1949.

It would seem that although repeated blood phosphatase and radiographic

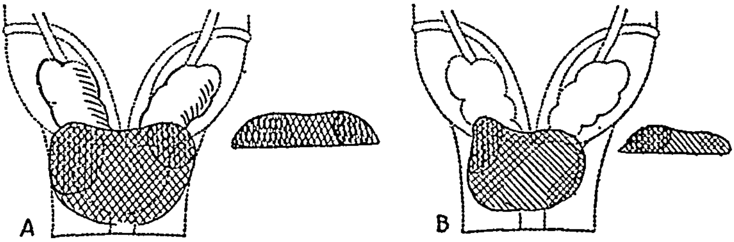

FIG. 3. *A*, situation at start of combined endocrine therapy June 12, 1948. *B*, condition at time of radical perineal prostatectomy March 15, 1949.

studies had been negative, metastasis had occurred before the radical prostatectomy was performed. Although at no time was there any evidence of a local recurrence, bone lesions were present within a year. The patient died of carcinomatosis on October 7, 1950. It now seems to us that the follow-up radical perineal prostatectomy is of very questionable value in those cases where extension beyond the vesical neck to the region of the trigone is present when the patient is first examined.

Case 4. G. O. B., S.M.H., 283183, aged 68, complained at the time of his first visit on September 20, 1948 of a gradually increasing frequency, nocturia, urgency and dribbling of 3 months' duration. The prostate was of third degree induration and greatly enlarged in its lateral and anteroposterior directions. Except for three very hard, discrete, nodular areas its posterior surface was relatively smooth. The median furrow and notch were absent. There was extension for a considerable distance up over each seminal vesicle with intervesicular plateau formation (fig. 4, *A*).

Following a bilateral orchiectomy on September 25, 1948, the patient was sent home on stilbestrol therapy with instructions to return at monthly intervals for observation. On March 14, 1949 the prostate had decreased to almost normal size and was of first degree induration. Second degree induration was present over the base of each seminal vesicle, more on the left than right, and between them there remained a plateau-like ridge of second degree induration (fig. 4, *B*).

A radical perineal prostatectomy was performed on March 17, 1949. The operator encountered marked difficulty in freeing the left seminal vesicle due to the presence of scar or carcinomatous tissue, probably the latter. He felt that extension beyond the operative field had occurred.

Active areas of carcinoma were found in sections from the prostatic and seminal vesicle portions of the surgical specimen. At the time of discharge, 30 days after operation, the patient occasionally dribbled slightly while at rest and considerably when under stress. Inasmuch as he was able to stop his stream completely during the act of voiding, we were confident that he would regain satisfactory control within a few weeks or months. Because of the relatively rapid progress of the disease the patient never returned for further observation. He died of carcinoma of the prostate on November 13, 1949.

In this patient at the time of operation there remained areas of second degree induration over the region formerly occupied by a well-defined intervesicular plateau due to extension from the prostatic carcinoma. In such cases the possi-

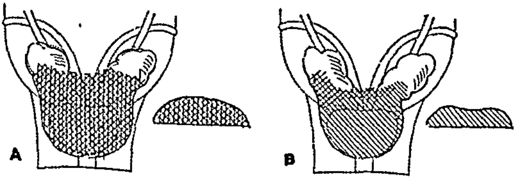

FIG. 4. *A*, prostatic involvement with extension to seminal vesicles when combined endocrine therapy was started September 9, 1948. *B*, induration due to cancer still present over seminal vesicles when radical perineal prostatectomy was performed March 14, 1949.

bilities of lymphatic and perineural extension or the presence of active tumor cells beyond the field of operation are such as to make the follow-up radical prostatectomy of very questionable value.

Case 5. V. M., S.M.H., 301085, aged 64 when first examined on August 29, 1949 complained of unusual fatique, decrease in size of stream, hesitancy and nocturia of 2 years' duration. Nothing of significance was found on physical examination except in the prostate gland which was moderately enlarged in all directions. Considerably more than half of the left lateral lobe was filled by a hard, irregular, fixed nodule that pushed its lateral border about 1.5 cm. beyond the confines of its normal contour and which extended medially almost to the median furrow (fig. 5, *A*).

Blood phosphatase and radiographic studies were negative for metastasis. Punch biopsy and Papanicolaou studies were positive for carcinoma.

The patient was placed on estinyl therapy 0.025 mg. three times a day and examined at monthly intervals until November 28, 1949. At that time the nodule seemed to have regressed sufficiently to permit its complete removal by radical surgery (fig. 5, *B*).

On cystoscopic examination the vesical neck simulated the picture of moderate collar hypertrophy. The residual urine was only 15 cc and there was no evidence of carcinoma extending into or beyond the vesical neck. On rectal palpation over the cystoscope an indurated nodule of moderate size was felt in the left lobe of prostate close to the apex. Although the outer border of the lobe was not well defined, the examiner thought there was a reasonable chance of getting around this area at operation.

On November 29, 1949 a radical perineal prostatectomy was performed. Considerable difficulty was encountered in developing a satisfactory line of cleavage between the lateral border of the left lobe of the prostate and the periprostatic tissue for a short distance just below the apex. However when this had been accomplished it appeared as though we had been able to get around the involved area.

His immediate postoperative course was very satisfactory. When he left the hospital 18 days after surgery his wound was healed and urinary control was good. He was sent home on estinyl 0.025 mg. daily, with instructions to return for a check on his condition at intervals of three months. A rectal examination on October 9, 1950 revealed a smooth operative field. His acid phosphatase was 5.1 and his alkaline 10.3 King-Armstrong units. On February 5, 1951 he returned

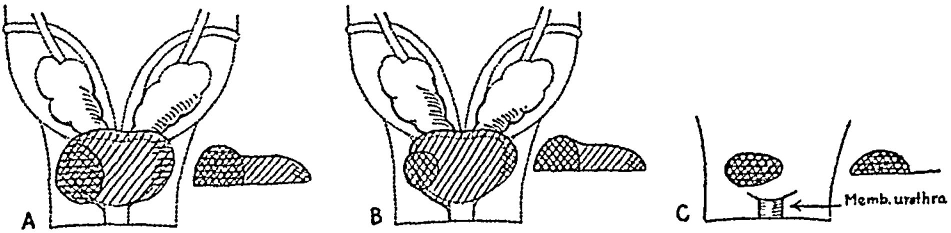

FIG. 5. *A*, extent of prostatic involvement when patient was first examined August 29, 1949. *B*, condition at time of radical perineal prostatectomy November 29, 1949. *C*, recurrence when first discovered February 5, 1951

with a story of increasing fatigue and pain along the course of the right sciatic nerve. A recurrent lesion was found that corresponded somewhat in size and position to the one which was present in the prostate at the time of his first examination (fig. 5, *C*). At this time his acid and alkaline phosphatase readings were 6.4 and 16.6 King-Armstrong units respectively. Radiographic studies were negative for metastasis.

The bilateral orchiectomy performed on February 6, 1951 was supplemented with estinyl therapy 0.05 mg. twice daily. The regression of the growth and the relief of pain were only temporary. In August 1951 the recurrence had increased in size and his right sacro-iliac and sciatic pain had become more severe. The pelvic mass shrunk to the size of a pea following 700 mg.-hr. of radium applied per rectum in fractional doses. On October 17, 1951, because the patient's pain was increasing and metastatic lesions were present, a course of deep x-ray therapy was started. The relief from this was quite temporary.

Because his symptoms, blood phosphatase, and radiographic studies indicated steady progress of the disease, the right adrenal was removed on February 7, 1952 and the left 11 days later. The disease continued to progress gradually and death occurred on August 8, 1952.

Judging from the pathological character and extent of growth in the surgical specimen there might have been a better chance for its complete extirpation had the preoperative treatment consisted of a bilateral orchiectomy in addition to the estinyl therapy and had it been prolonged up to the point of maximum regression of the carcinomatous lesion.

DISCUSSION AND RESULTS

Because in some cases of carcinoma of the prostate in which the response to endocrine therapy has been especially satisfactory it may be very difficult to demonstrate the presence of residual carcinoma by means of microscopical studies of sections from the surgical specimen, the operator who is unwilling to proceed with radical surgery without positive histopathological support should make these studies before starting treatment. In 19 of our cases the clinical impression of carcinoma was confirmed by biopsy studies made either before or very shortly after endocrine therapy had been instituted. In 3 cases carcinoma was found in the surgical specimen even though biopsy studies were negative. Pathological studies of a biopsy specimen obtained from the first patient in this series on his initial visit were typical of carcinoma of the prostate. Following castration and estrogen therapy the radical operation was performed 42 months later. A study of many sections from the surgical specimen repeatedly showed connective tissue formations very similar to those found in cancer of the prostate but the epithelial cells were either absent or so changed that a positive diagnosis could not be made. It is our belief that had a serial section of the whole surgical specimen been made, carcinoma cells would have been found. In 2 recent cases a clinical impression upon rectal examination by at least two of our senior staff, repeated positive Papanicolaou studies by a cytologist especially skilled in this particular field, and regression and softening of the suspected area following endocrine therapy, all pointed so strongly towards carcinoma that a radical perineal prostatectomy was performed.

Pathological studies of a considerable number of sections from each surgical specimen showed the pattern described above but no typical normal carcinoma cells were found. It is interesting that the cytologic studies in these cases showed progressive effect of the endocrine therapy upon the malignant cells which were very plentiful when the patients were first examined. In one case after 6 months of therapy, the malignant cells completely disappeared and remained absent until the radical operation was performed 2 months later. While the malignant cells did not completely disappear in the second case, they did decrease greatly in number and show marked estrogen effect before the operation.

In our opinion, all patients who have had a radical prostatectomy for cancer of the prostate gland should continue a routine course of some type of estrogenic therapy for a very long time after operation, regardless as to whether they were treated in the manner presented above or belonged to the more fortunate group, in which because of the size and location of the carcinomatous nodule, a preliminary course of endocrine therapy did not seem necessary. It is not always easy to convince some of these patients, who are feeling well and know that the organ which was the source of their trouble has been completely removed, that they must continue estrogen therapy even though at times it may cause some discomfort. However, the reasons for the postoperative continuance of estrogen therapy are so obvious and valid that even the most stubborn patient can be convinced of its necessity without creating a cancer phobia, if patience and discretion are exercised in their presentation.

When the clinical impression of carcinoma of the prostate has been definitely confirmed by a positive punch biopsy study in a patient who qualifies for the follow-up radical perineal prostatectomy providing the response to hormone control treatment proves to be successful, bilateral orchiectomy plus estrogen is the preoperative therapy of choice. As shown by Nesbit and Baum, the survival rate was better where these two types of endocrine therapy were combined than when either was used alone (table 1). Furthermore it seems to us that the cleavage lines are more easily developed and the whole operative procedure somewhat facilitated in the presence of a previous bilateral orchiectomy. Finally any lapse on the part of the patient with reference to his postoperative estrogen therapy might be covered, for a time at least, by the absence of the testicles.

The results of endocrine therapy plus a radical perineal prostatectomy in our first 25 cases have been most encouraging. In all these cases treatment was started 36 months or more before the material for this report was summarized. The longest time that had elapsed since endocrine therapy was started was 130 months, the shortest 14 months and the average time was 61.2 months. The average time after prostatectomy was 47.6 months, the longest 89 and the shortest 5 months. There were 4 deaths within 36 months from the time that the therapy was started. In one where carcinomatous tissue was left in the seminal vesicle region (case 4) the patient died of cancer 14 months after treatment was started and 5 months after surgery. Another patient died of coronary

TABLE 1. *Percentage survival at 6 month intervals of a series of 25 selected cases of advanced carcinoma of prostate without metastasis at time of first visit which were treated by endocrine therapy alone or combined with radical perineal prostatectomy as compared to a control series of similar cases (Nesbit and Plumb) treated by methods in use before introduction of endocrine therapy.*

TYPE OF THERAPY	MONTHS						NUMBER OF ELIGIBLE CASES	PER CENT DEAD NOT DUE TO CA.
	6	12	18	24	30	36		
Control (Nesbit and Plumb)	72.0	54.0	39.0	32.0	25.0	20.0	273	—
Stilbestrol (Nesbit and Baum)	90.7	82.2	75.6	69.1	56.2	49.7	143	34
Castration (Nesbit and Baum)	91.6	84.9	74.0	65.9	62.2	53.4	239	26
Castration and Stilbestrol (Nesbit and Baum)	95.6	89.3	82.3	76.0	76.0	66.0	159	37
Endocrine therapy plus the radical perineal prostatectomy (Scott)	100	100	92.0	88.0	84.0	84.0	25	25
Total cases							839	

thrombosis 14 months after therapy was instituted and 8 months after prostatectomy. A very careful autopsy study revealed neither local recurrence nor metastasis. In the third patient (case 3) who died of metastases 28 months after the start of treatment and 18 months after his radical operation there was no evidence of local recurrence. The fourth patient who developed a reccurent lesion with metastasis was not greatly benefited by bilateral orchiectomy, deep x-ray therapy and bilateral adrenalectomy, dying of carcinomatosis 35 months after therapy was started.

Of the patients who survived 3 years or more after treatment was started 5 are known to be dead. There were two deaths due to recurrent and metastatic carcinoma from the prostate. One of these patients who died 82 months after start of therapy was not placed on estrogen therapy until a local recurrence was discovered 56 months after his prostatectomy (case 1, C). The other patient died of generalized carcinomatosis 62 months after he was placed on treatment. A third patient died of a primary carcinoma of the stomach 64 months after treatment was instituted while the fourth died of coronary disease 58 months after therapy was started. A fatal airplane accident 47 months after start of therapy resulted in the death of the fifth patient. In another patient who refused to take postoperative estrogen therapy and in whom a small, local, recurrent nodule was suspected 46 months after treatment was started, the area completely disappeared following orchiectomy and needle radiation therapy. When last seen 10 months later all studies were negative for cancer. Of the remaining 6 patients who have been followed less than 36 months one has developed a local recurrence and metastases.

Before attempting to evaluate the relative effectiveness of endocrine therapy plus the follow-up radical perineal prostatectomy in the treatment of carcinoma of the prostate, it seems advisable to emphasize that its field of usefulness is definitely restricted. It is our belief that in early carcinoma of the prostate where the lesion is contained within the confines of the prostate, the radical removal of the gland, seminal vesicles along with their posterior fascial covering should be accomplished as soon as possible after the diagnosis has been made. As pointed out previously the patients for whom the combined therapy offers the most hope are very carefully selected from the group of advanced carcinoma of the prostate who were without metastasis when first seen.

Fortunately, there is now available sufficient reliable data to permit a very satisfactory evaluation of the relative effectiveness of the various types of therapy used in the treatment of patients with advanced carcinoma of the prostate who were without metastasis when first seen. As a control series we have the report by Nesbit and Plumb on the survival rate at 6 month intervals on 273 of these cases which were treated by the methods in use before the introduction of endocrine therapy and followed for 36 months after their first visit. Based upon case material supplied by members of the Urosurgical Society, Nesbit and Baum in 1952 reported the survival rate at 6 month intervals for 36 months on a series of 540 cases of advanced carcinoma of the prostate without metastasis when first seen which were treated by the various types of endocrine therapy in common use to-day. To the above we have added our series of 25 cases which were treated by the combined therapy (table 1). One cannot examine these results without experiencing a feeling of profound gratitude for the progress that has been made in the treatment of carcinoma of the prostate during this last decade. Whereas the survival rate for 36 months was but 20 per cent in the control series, it was 66 per cent in the castration and stilbestrol group and 84 per cent in the patients who were treated by the combined endocrine and radical prostatectomy method. While we realize it would be unwise to attach too much significance to the results of a comparative study in which one group is much smaller than the others, it is interesting to note that the per cent of deaths not due to cancer in the small group was very close to that of the other groups.

We think that our results are sufficiently encouraging to warrant further trial of this therapy. Even if in our future cases the carcinoma is not as satisfactorily controlled, we believe that this treatment in most instances, where judiciously used, will prolong the life of the patient and increase his period of freedom from the distressing urinary symptoms that almost inevitably accompany the late stages of this disease. As pointed out previously, the operation entails little or no more risk than other open operations for relief of prostatic obstruction. Furthermore, the introduction by Vest of the traction suture method of anastomosing the vesical neck and the membranous urethra has done much to prevent the incontinence that occasionally resulted from this type of surgery.

CONCLUSIONS

The results obtained in the first 25 of a series of 31 selected cases of advanced carcinoma of the prostate that were treated by endocrine therapy combined with a follow-up, radical perineal prostatectomy and followed three years or more have been presented and discussed.

While this report has not been submitted as an evaluation of the ultimate mortality in such cases, we believe the results to date warrant a further trial of this therapy, not only by us, but by others.

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ENDOCRINE INHIBITION AS RELATED TO CARCINOMA OF THE PROSTATE

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The prostate is an androgen target organ. Its normal growth and function are stimulated by testosterone. The growth of the neoplastic prostate may be stimulated by androgenic activity. For 11 years, extensive observations have been made concerning the benefits of orchiectomy and estrogen administration in the treatment of patients with carcinoma of the prostate. The anti-androgen approach obtains dramatic results in some 60 per cent of patients with disseminated carcinoma of the prostate. These patients, however, almost invariably have a relapse and are usually the eventual victims of cancer.

There has been widespread investigation as to the source of extragenital androgens which could be responsible for the reactivation of these carcinomas. The reticular zone of the adrenal cortex is a known androgen producer and its secretions, at least in certain pathological conditions, are capable of creating radical changes in the secondary sexual characteristics. In 1945, Huggins and Scott first performed bilateral adrenalectomy on patients with relapsing carcinomas of the prostate.[1] Inadequate adrenal replacement therapy made this procedure impractical until cortisone became available in 1951. Since then Huggins and Bergenstal have reported 14 cases of bilateral adrenalectomies on patients with relapsing carcinoma of the breast and prostate.[2] Many clinics throughout the country at this time are doing bilateral adrenalectomy for carcinoma of the breast and prostate.

Early observations with cortisone showed that excessive or prolonged use would suppress endogenous adrenal function.[3] Wilkins and his associates showed that as little as 25 mg. of cortisone acetate given orally each day would suppress excessive androgen production in patients with adrenal cortical hyperplasia.[4] In 1951 we began using cortisone to treat patients with relapsing carcinoma of the prostate. It was our hope to suppress adrenal androgen production and to gain a remission in patients previously shown to have been benefited by anti-androgen therapy. Cortisone was given in combination with stilbestrol in an effort to suppress the formation of gonadotrophins as well as suppressing adrenal function. We shall show later why we feel this is important.

Huggins has compared the pituitary-gonadal relationship to a closed-cycle

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Read at annual meeting, South Central Section of American Urological Association, Kansas City, Mo. September 21–23, 1953.

Cortone acetate generously supplied by Merck and Company.
Aided in part by Public Health Grant #H-1653 (C-3).

[1] Huggins, C. and Scott, W. W.: Bilateral adrenalectomy in prostatic cancer. Ann. Surg., **122:** 1031–1041, 1945.

[2] Huggins, C. and Bergenstal, D. M.: Inhibition of human mammary and prostatic cancers by adrenalectomy. Cancer Res., **12:** 134–141, 1952.

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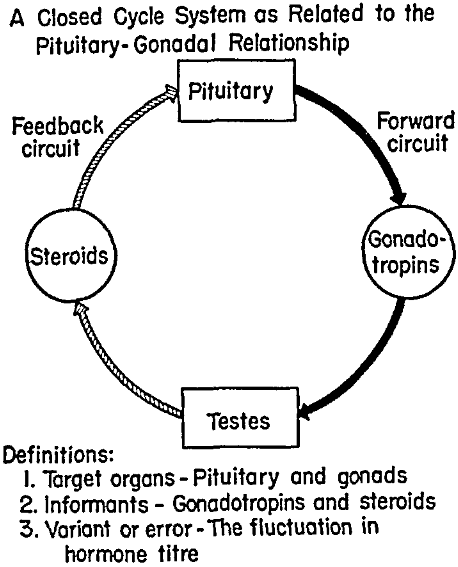
A Closed Cycle System as Related to the Pituitary-Gonadal Relationship
Pituitary
Forward circuit
Gonado-tropins
Testes
Steroids
Feedback circuit
Definitions:
1. Target organs - Pituitary and gonads
2. Informants - Gonadotropins and steroids
3. Variant or error - The fluctuation in hormone titre

FIG. 1

feed-back electrical circuit.[5] This is indeed an interesting speculation. It is realized, of course, that the human being does not respond in a linear fashion and the effects are not always proportional to the causes. Regardless of this, it is stimulating to inspect the endocrine system in relation to certain rules of feed-back.

In a closed-cycle feed-back system (fig. 1), the variant or error causes the target to measure, compare, and correct so that the actual value is changed to the desired value. If the input oscillates in value, then the output quantity will also oscillate in value. This causes successive quantities around the loop to oscillate. When the time lag of the response adds up to one-half the cycle, the feed-back maintains its assumed motion. By increasing the amount of the informant, oscillation is increased and by increasing the frequency of the informant, there is an increase in the time lag of the response. The mechanical methods to prevent these dilemmas are to quicken the target response, divide the target into many points of action, and to develop target anticipation or time lead. The nervous system is an example of time lead. The output impulses occur before the maximal stimulus, thus preventing overshooting or oscillation.

In the pituitary-gonadal system, we have a complex group of feed-backs which for the most part are unmeasurable and little understood. It is possible that order is maintained in this system by dividing the point of action over a number of functioning cells or by damping the informant by modifications occurring in the

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Early observations with cortisone showed that excessive or prolonged use would suppress endogenous adrenal function.[3] Wilkins and his associates showed that as little as 25 mg. of cortisone acetate given orally each day would suppress excessive androgen production in patients with adrenal cortical hyperplasia.[4] In 1951 we began using cortisone to treat patients with relapsing carcinoma of the prostate. It was our hope to suppress adrenal androgen production and to gain a remission in patients previously shown to have been benefited by anti-androgen therapy. Cortisone was given in combination with stilbestrol in an effort to suppress the formation of gonadotrophins as well as suppressing adrenal function. We shall show later why we feel this is important.

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TABLE 1.—*Living Patients*

PATIENT	TUR AND ORCHIECTOMY	LENGTH OF STILBESTROL ℞ UNTIL RELAPSE	LENGTH OF CORTISONE ℞ IN MG				COMPLICATIONS	RESULTS
			Over 300	200	100	25–50		
1. W. C. Age 66 C. male	May '52	10 mo.	21 d.	2 d.	3 d.	5 mo.	Edema and cardiac failure	Pain free. Acid phosphatase dropped from 1.7 to .8 mm.
			Total 6 mo.					
2. J. B. Age 57 W. male	May '51 Nov. '51	3 mo.	15 d.	0	47 d.	17 mo.	Edema Bleeding ulcer	Symptomatically well. Pain free. Acid phosphatase normal
			Total 19 mo.					
3. V. T. Age 66 C. male	Jan. '47	75 mo.	5 d.	7 d.	8 d.	12 mo.	None	Pain free. Acid phosphatase normal
			Total 13 mo.					
4. O. E. Age 64 W. male	May '51 May '52	7 mo.	17 d.	2 d.	3 d.	7½ mo.	None	Pain free. Acid phosphatase dropped from 6.0 mm. to 2.1 mm.
			Total 8½ mo.					
5. A. T. Age 75 W. male	Feb. '52	0	42 d.	3 d.	8 d.	17 mo.	Edema	Symptomatically well. Pain free. Acid phosphatase normal
			Total 19 mo.					

Cortisone inhibits adrenal cortical function by inhibiting the adrenocorticotrophic hormone of the anterior pituitary. There is some evidence that cortisone may inhibit the production of the luteinizing hormone.[10] Sohval and Soffer have demonstrated that cortisone causes an increase in the urinary excretion of follicle stimulating hormone.[11] Since cortisone inhibits ACTH and possibly the luteinizing hormone, and stilbestrol inhibits the follicle stimulating hormone, it would appear that the combination of cortisone and stilbestrol would not only inhibit endogenous adrenal function but would also inhibit the production of gonadotrophins. Neither cortisone or stilbestrol by itself could satisfactorily perform this function. The gonadotrophins, we feel, are either directly or indirectly the prime source of stimulus to the endocrine responsive tumors and hence should be a prime target in therapy.

Twelve patients with relapsing carcinoma of the prostate were treated with a combination of cortisone and stilbestrol. All but one of the patients had previous orchiectomy and stilbestrol therapy. The length of time elapsed since the institution of orchiectomy and stilbestrol therapy varied from 3 to 75 months with an average of 20.2 months. This indicates that patients, all of whom had metastatic carcinoma of the prostate at the time of their original diagnosis, had gone for an average of 20.2 months until they had relapses. The age in this group varied from 57 to 75 with an average age of 65.5. There were 8 white patients and 4 Negros treated. Eight of these patients had elevated acid phosphatases and all of the patients had either osteoblastic or osteolytic metastases.

Tables 1 and 2 briefly summarize the course, length of treatment and results obtained from treatment. As will be noticed, treatment consisted of varying

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TABLE 2.—*Dead Patients*

PATIENT	TUR AND ORCHIECTOMY	LENGTH OF STILBESTROL ℞ UNTIL RELAPSE	LENGTH OF CORTISONE ℞ IN MG				COMPLICATIONS	RESULTS
			Over 300	200	100	25–50		
1. J. M. Age 65 W. male	June '49 Dec. '49	35 mo.	56 d.	7 d.	9 d.	0	Salt retention Edema Pneumonia	Expired on 1-20-53 of influenza and bronchopneumonia
			Total 2½ mo.					
2. W. M. Age 75 W. male	Nov. '51 Dec. '51	11 mo.	55 d.	2 d.	11 d.	0	Salt retention Edema Nasal infection Influenza	Expired on 1-25-53 of carcinomatosis and influenza
			Total 2½ mo.					
3. A. G. Age 65 C. male	Jan. '52	8 mo.	30 d.	16 d.	12 d.	1 mo.	Tuberculosis activation	Expired suddenly of coronary thrombosis
			Total 3 mo.					
4. E. T. Age 66 W. male	March '51	9 mo.	34 d.	4 d.	21 d.	4 mo.	Edema Salt retention Cardiac failure	Expired after cortisone stopped by patient
			Total 6 mo.					
5. R. N. Age 67 W. male	June '50 July '50	15 mo.	12 d.	2 d.	11 d.	8 mo.	Salt retention Edema Cardiac failure	Expired of pneumonia after cortisone stopped by patient
			Total 9 mo.					
6. S. C. Age 70 W. male	June '49	33 mo.	17 d.	0	0	5 mo.	Marked edema Cardiac failure	At no time showed clinical improvement
			Total 6 mo.					
7. R. S. Age 60 W. male	Jan. '51 Feb. '52	6 mo.	61 d.	5 d.	10 d.	10½ mo.	Salt retention Edema	Expired July '53
			Total 13 mo.					

dosage of cortisone given with stilbestrol. Any dose of cortisone over 100 mg. a day was considered to be in the therapeutic range and doses over 300 mg. per day in the toxic range. As has been previously stated, it was our desire not only to cause adrenal inhibition, but also to inhibit the anterior pituitary. An initial dose of cortisone of 300 mg. or over was given for as long as 61 days and doses of 100 mg. or over were continued for as long as 76 days. The patients were then placed on maintenance doses of 25–50 mg. of cortisone and 5 mg. of stilbestrol. These medications were to be continued for the rest of their lives.

The subjective results showed marked relief of pain and, generally speaking, increased vigor and activity. Pain relief continued beyond the large doses of cortisone and was just as marked on maintenance levels. Several patients experienced pain when stilbestrol was stopped even though they were still on cortisone therapy.

Objectively, these patients showed little change in the size or shape of their prostates. Their hemoglobin remained the same and other than from edema, there was little actual weight gain. Bony metastases as shown by x-ray showed regression in only one case. The acid phosphatase levels fell in 8 out of 12 cases. The response of the acid phosphatase to treatment appears to depend on a combination of cortisone and stilbestrol therapy, as will be discussed in more detail later.

Five patients in this series are still living and relatively well. Three of these patients are what might be classified as clinical remissions. Two of these patients have gone 19 months since the institution of therapy.

Seven patients have expired since treatment was begun, either from their original carcinomas or some complicating factors. The complications on large doses of cortisone are frequent and severe. Two patients in this series expired after they had inadvertently stopped cortisone for a period of one to two weeks. One of the two was admitted to the hospital in extremis and expired with all of the clinical signs of adrenal insufficiency. Three patients developed influenza while on therapy. Their clinical course was severe, in spite of antibiotics and supportive therapy; two of these patients expired. Two patients died of progressive carcinoma and one patient died of a coronary thrombosis after he was in an apparent clinical remission.

An effort to follow the activity of the carcinoma was made by frequent acid phosphatase readings. At first it was distressing to note that on large doses of cortisone alone the acid phosphatase actually went up. Later it was found that when stilbestrol was added and the cortisone dropped to maintenance levels, the acid phosphatase dropped to normal or far below precortisone levels. Since these patients had previously been on stilbestrol and the acid phosphatase levels were better than those of pretreatment level, it became apparent that cortisone and stilbestrol must have some synergistic reaction in inhibiting tumor activity. Figure 3 shows the precortisone and maintenance cortisone levels of acid phosphatase.

Figures 4 and 5 graphically show the course of the alkaline and acid phosphatase of two typical patients while on therapy. They illustrate that the acid phosphatase did not return to normal until maintenance levels of cortisone were reached.

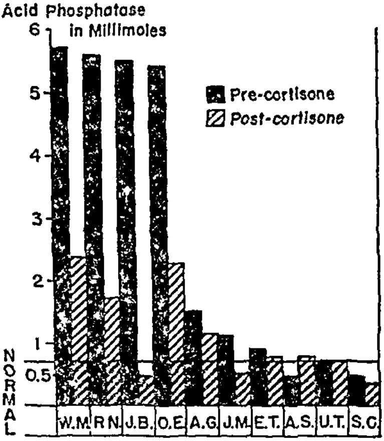

FIG. 3

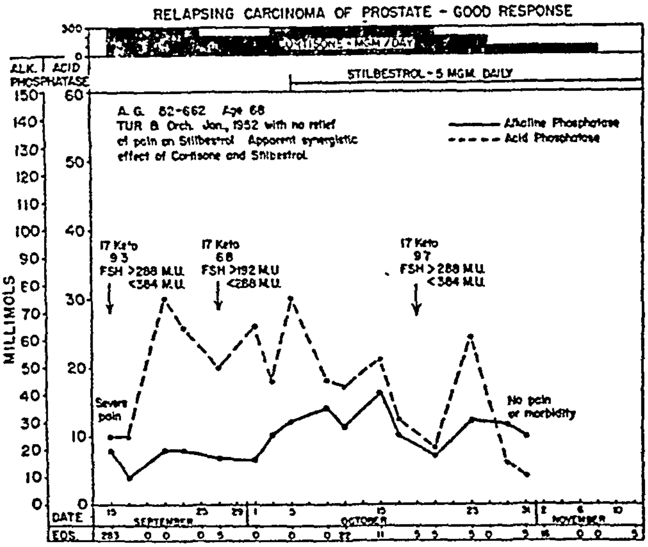

FIG. 4

Seventeen-ketosteroid studies were made at regular intervals in all patients. Table 3 shows the steroid pattern in 9 pre- and post-cortisone-estrogen treated patients. Cortisone is broken down in part and excreted as 17-ketosteroids in the urine. This will increase the urinary excretion of 17-ketosteroids. While on large dosage of cortisone, the steroid levels were usually fairly high. After maintenance levels were reached, however, in most instances the steroids fell. In the one patient who stopped taking cortisone, there was only .9 mg. of ketosteroids excreted in 24 hours, indicating almost total adrenal inhibition.

Assay of the gonadotrophins was attempted, but considered unreliable. Ideally a more specific manner of measurement of the gonadotrophins is necessary before these changes can be properly evaluated.

In this series cortisone was used in excessive dosage. For this reason, we

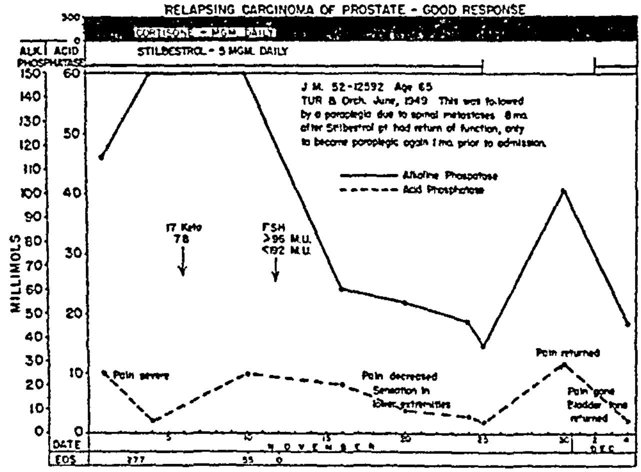

FIG. 5

TABLE 3 *17 Ketosteroid excretion before cortisone estrogen treatment and while on maintenance dosage*

PATIENT	PRE TREATMENT LEVEL IN MG	MAINTENANCE LEVEL IN MG
W M	4 3	2 1
E T	8 6	9
J M	7 8	15 0
R S	4 4	4 8
V T	8 0	1 7
J B	20 8	3 52
W C	13 1	4 7
A T	20 85	4 6
O E	9 9	6 2

observed many toxic responses In large doses, cortisone causes salt retention, edema, and potassium loss All patients were given 3 gm potassium chloride per day and all had salt-restricted diets In spite of this, edema occurred in 8 of our 12 patients Mercurial diuretics were used periodically to combat edema but it was found that the edema was unusually persistent and did not readily respond to diuretics It was necessary to digitalize 4 patients in whom cardiac failure developed co existent with their edema

Diminished resistance to stress was probably the most severe complication that occurred As has been previously stated, two of our patients died of influenza Intermittent antibiotics were given most of the patients as a prophylaxis against intercurrent infection Two patients died after stopping cortisone, presumably of adrenal insufficiency Certainly any patient taking cortisone should be warned of this grave consequence and if it is necessary to stop cortisone for any reason, several days of ACTH therapy should be given The patients' adrenal function should then be checked with periodic Thorn tests to determine adrenal status

Cortisone causes an increased secretion of hydrochloric acid, and gastritis developed in a number of patients One patient had a bleeding peptic ulcer while on therapy Routine antacids are now given in an effort to prevent this complication

One patient with an old fibrotic lesion in the apex of the right lung had soften-

TABLE 4

1 Bilateral orchiectomy
2 Estrogen stilbestrol 5 mg /day for life
3 Cortisone—300 mg /day for 2 weeks
200 mg /day for 2 weeks
100 mg /day for 2 weeks
25 mg /day for life
a Low salt diet
b KCl 2–3 gm daily
c Antacid regimen if ulcer history
d Diuretics as needed

ing and what the roentgenologist interpreted as activation of an old tuberculous lesion.

All patients showed slight early euphoria, but in no incidence were there any overt psychoses. Skin petechiae occurred in 4 patients. Osteoporosis was not marked while on a high protein intake. Most of these patients had an unusually good appetite and maintained a good nutritional status. No temporary or permanent hypertension or diabetes developed in any patient.

SUMMARY

Twelve patients with far-advanced relapsing carcinoma of the prostate were treated with a combination of cortisone and stilbestrol. The initial cortisone dosage given was high in an attempt to inhibit functionally the adrenal and the anterior pituitary. Stilbestrol was given as a necessary adjunct to pituitary inhibition.

Five patients are living and three of these are totally asymptomatic. Seven patients are dead; death occurred from progressive carcinomatosis or complications of therapy. The toxic responses to large doses of cortisone are frequent and severe. Urinary excretion of 17-ketosteroids was markedly depressed in 7 of 12 patients treated with cortisone and stilbestrol, indicating adrenal cortical inhibition.

Table 4 summarizes our regimen of treatment and necessary prophylactic measures.

It would appear from our small series of cases that about 40 per cent of the patients with far-advanced carcinoma of the prostate can obtain additional benefits from combination cortisone and stilbestrol therapy. These benefits are a great help in treating patients who have become refractory after previous orchiectomy and stilbestrol therapy.

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LATE RESULTS OF BILATERAL ADRENALECTOMY FOR ADVANCED CARCINOMA OF THE PROSTATE GLAND

WILLIAM J. BAKER

One year ago, a report was given to this Association on bilateral adrenalectomy for 10 patients whose carcinoma of the prostate gland and symptoms had not been adequately controlled by open prostatic surgery or revision of the obstructive vesical neck, estrogens, bilateral orchiectomy, with and without deep roentgen therapy, and oral cortisone. All of these patients were bedridden and required some form of opiate for their pain and discomfort. All patients had had a tissue diagnosis of cancer of the prostate gland. All patients had bone metastases. There was no immediate operative mortality. There was no difficulty in the postoperative management of these Addisonian individuals.

We have been impressed with the comfortable states of the majority of these patients after bilateral adrenalectomy. Only one patient failed to get relief from the procedure. All, except two, became ambulatory and euphoric. To be sure, there has been a recurrence of pain in all except one patient. He is alive and well almost 10 months. The recurrent pain has usually been less severe than the original pain. The patients who require small amounts of analgesic for their recurrent pain, have led a much more comfortable existence than they did before bilateral adrenalectomy. In 2 patients, whose pain returned, a short course of deep x-ray therapy over the painful regions, gave almost complete relief. X-ray therapy over these same regions, before bilateral adrenalectomy, had given no relief.

The youngest patient in this group was 47 years, the oldest was 76 years. The patients who have lived the longest after bilateral adrenalectomy were 57, 58, 60 and 61 years old. The age of the patient could not be related to the amount of relief which was obtained from metastatic pain. The patient who obtained no relief from the procedure was 59 years old.

Adrenalectomy for cancer is predicated on the fact that the adrenal gland is involved in the growth of neoplastic tissue. It is known that people with cancer have abnormal amounts of normal adrenal steroids. It is also known that people with cancer have steroids that are not found in other people. However, after bilateral adrenalectomy in patients with advanced cancer of the prostate gland, serial x-rays of osseous lesions, serial acid and alkaline phosphatase determinations, serial rectal examinations, serial body weight and hemoglobin determinations and serial androgen values have furnished us no evidence that the prostatic cancer or its metastases have been inhibited. As far as we can ascertain, the cancer continues to grow at its usual rate. Figure 1, *A* is the picture of obvious metastastic bone lesions of one of these patients before bilateral adrenalectomy. Figure 1, *B* is a picture of the same lesions 7 months after bilateral adrenalectomy. Figure 2, *A* is the x-ray picture of obvious metastatic bone lesions of another patient before bilateral adrenalectomy. Figure 2, *B* is a repeat picture of this same patient 9½ months after bilateral adrenalectomy. Figure 3 is the final

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Read at annual meeting, American Association of Genito-Urinary Surgeons, Hot Springs, Va. May 6–8, 1953.

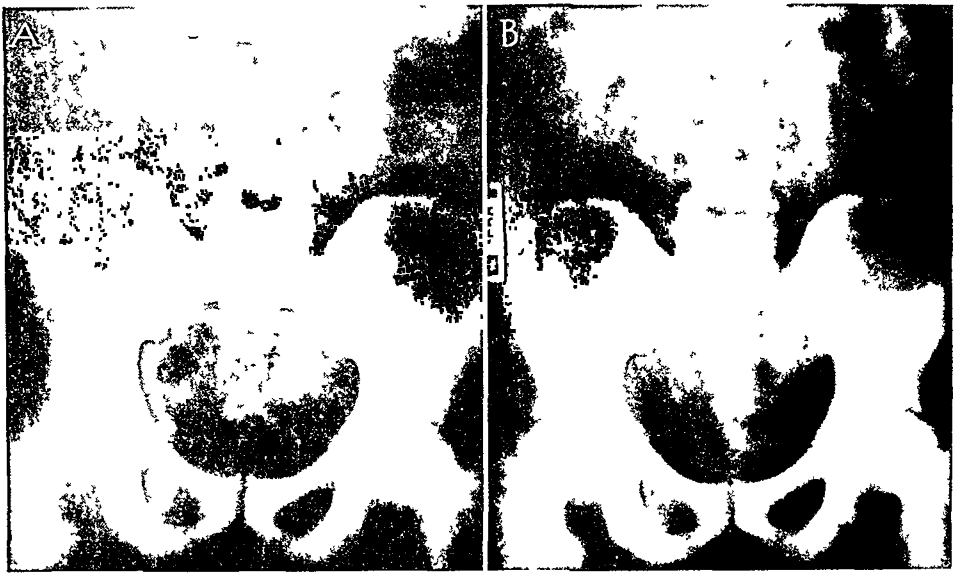

Fig. 1

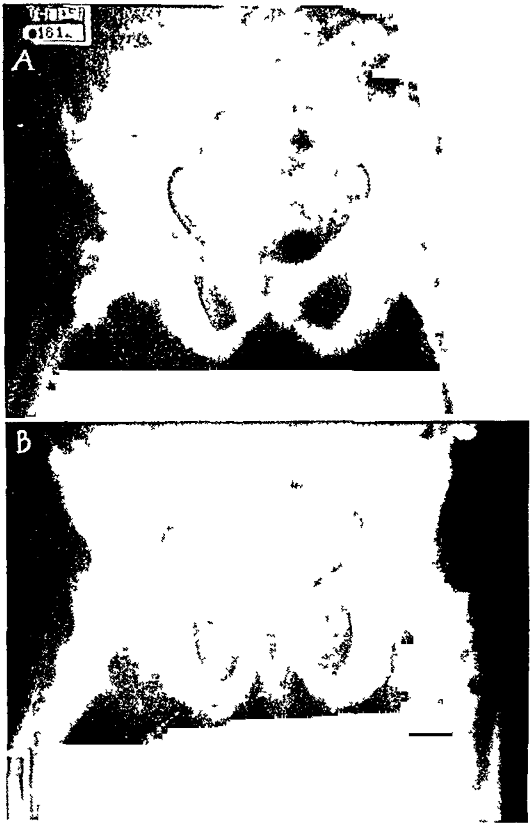

Fig. 2

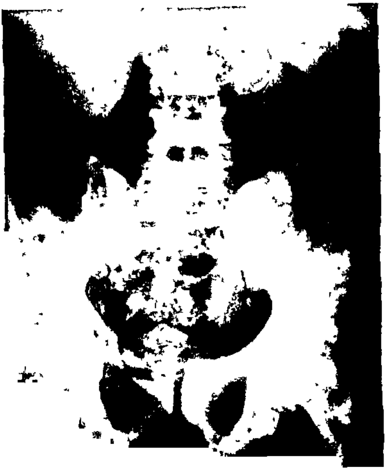

FIG. 3

picture of this patient's bones just before he died, or 13 months after bilateral adrenalectomy. The metastatic bone lesions of these two patients were obviously not retarded. It is certain that no bone metastases disappeared in these pictures. It must be admitted that, occasionally, bony metastases seem to grow more sclerotic after adrenalectomy. We have never seen them become smaller or disappear.

What about the life expectancy of the man with advanced prostatic cancer, who has had bilateral adrenalectomy? Tables 1 and 2 show that only two out of eleven of our patients are alive. The longest time that any of our patients lived after this procedure is 1 year, 1 month, 11 days. One patient is alive 1 year, 22 days after the procedure. This man has recently complained of severe pain which requires Demerol for control. Another patient is alive 9 months, 20 days. He had minimal persistent discomfort after bilateral adrenalectomy. A course of deep roentgen therapy caused complete disappearance of the discomfort. He takes no sedatives or analgesics, is ambulatory, euphoric and working. The other 9 patients lived from 1½ months to 1 year, 11 days. Thus, it can be seen that there has been no striking prolongation of life in this group.

All of our patients have died relatively suddenly. They were ambulatory one day and in a terminal state the next day. Most of them have become weak, apathetic and finally comatose, all within a very few hours. Blood chemistry studies have not revealed striking changes even on the day of death.

Four complete autopsies have been performed on patients who have had bilateral adrenalectomy for advanced prostatic cancer. No residual adrenal tissue was found in these four bodies. No tissue had been spared from invasion by the cancer cells.

TABLE 1. *Late results of bilateral adrenalectomy for advanced carcinoma of the prostate gland*

RACE	AGE	SURVIVAL TIME	NARCOTICS REQUIRED	TYPE OF DEATH	AUTOPSY—REMARKS
T. P., Negro, St. Luke's Hospital	48	6 months 1 day	Needed codein last month of life	Collapsed suddenly and died in 2 hours	Generalized carcinomatosis. No other adrenal tissue found
I. S., White, Cook County Hospital	59	5 months 3 days	Demerol the last 4 months of life	Generalized edema and coma last 2 days of life	Generalized carcinomatosis. Metastases in pituitary gland. No other adrenal tissue found
C. G., Negro, Cook County Hospital	61	1 year 1 month 11 days	Required codein and Demerol last 3 months of life	Developed very severe anemia. Many transfusions. Always euphoric. Sudden death	No autopsy
B. T. W., Negro, Cook County Hospital	47	3 months 5 days	Demerol last 2 months of life	Died suddenly. In coma for 2 hours	Generalized metastases. Large metastatic growth around old gunshot wound of hip. No adrenal tissue found
J. M., Negro, Cook County Hospital	57	1 year 1 day	Demerol last 6 weeks of life	Always had troublesome gas "on stomach". Died during sleep	Generalized metastases. Each ureter was partially obstructed by a metastatic tumor. Original blood pressure 220/110. Adrenalectomy did not alter hypertension. No adrenal tissue found

TABLE 2. *Late results of bilateral adrenalectomy for advanced carcinoma of the prostate gland*

RACE	AGE	SURVIVAL TIME	NARCOTICS REQUIRED	TYPE OF DEATH	AUTOPSY—REMARKS
A. N., White, St. Luke's Hospital	65	6 months 9 days	Demerol required last 4 months of life	Died very suddenly. Ambulatory until day of death	No autopsy
S. G., White, St. Luke's Hospital	76	5 months 9 days	Codein required last 2 weeks of life	Sudden collapse and death while campaigning for Taft	No autopsy
E. N., White, Cook County Hospital	60	Still alive and well. 1 year 22 days	Has fleeting pains. Takes no sedatives		
C. B., White, St. Luke's Hospital	62	1 month 15 days	No sedatives required	Lethargic and catatonic for 6 weeks. Slow death	No autopsy
J. Z., White, St. Luke's Hospital	54	3 months 10 days	No relief from metastatic pain	Sudden death. One hour of coma	No autopsy
T. T., Japanese, Cook County Hospital	58	Still alive and well. 9 months 20 days	No sedatives required		Complete relief from pain after x-ray therapy following adrenalectomy

It can be seen that the evaluation of this procedure is made entirely on the subjective response of the patient. The relief of pain is usually striking. The patients who have been bedfast because of pain, feel better almost immediately and want to get out of bed in a few days. Their appetite becomes ravenous and the replacement therapy with cortisone usually produces an euphoric state. The occasional patient will be rehabilitated enough to resume his former work. Most of our patients have never returned to their work.

The past year has brought to our attention that the patient who fits our indication for this procedure has become very scarce.

Cook County Hospital is a haven for end pathology. It has furnished us only one patient for our series. Four excellent residents have endeavored to find such patients. St. Luke's Hospital has not furnished a single private patient for our series. One wonders whether prostatic cancer is changing its biological behavior.

It is believed that bilateral adrenalectomy is an excellent procedure for the relief of metastatic pain from advanced prostatic cancer of patients whose pain is not adequately controlled by castration, estrogens, deep roentgen therapy or oral cortisone.

In conclusion, the thought should be left with you that there is evidence that some cancers of the prostate gland seem to be independent of androgens and the search for related stimulating or inhibiting factors should be continued diligently.

7 W. Madison St., Chicago 2, Ill.

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APPRAISAL OF PRESENT METHODS OF TREATMENT OF ADVANCED PROSTATIC CANCER

W. W. SCOTT

From the James Buchanan Brady Urological Institute, the Johns Hopkins Hospital, Baltimore, Md.

Until receipt of the program for this meeting and particularly until I had read the titles of the papers constituting this symposium, I had little idea as to what I should present under the title which Dr. Heckel assigned to me.

Dr. Scott has just presented to you an evaluation of hormonal therapy followed by radical perineal prostatectomy in selected cases of advanced carcinoma of the prostate. You will recall that Dr. Colston and Dr. Brendler, of our Institute, presented a preliminary report on this subject in an issue of the J.A.M.A. for 1946. Whereas I believe that Dr. Scott has handled the subject in a splendid fashion and has demonstrated the merits of this regimen in certain selected cases, I am of the opinion that in this instance, as well as in all instances of studies involving the treatment of cancer of the prostate, insufficient attention has been paid to the "biological potential" of the cancer. Admittedly, we have used almost all of the yardsticks available to us at present, but none really tell us the degree of malignancy of any given cancer, and hence are of little prognostic value.

May I attempt to illustrate what I am driving at by referring to two patients recently seen again at the Brady Institute: The first, a man aged 75, was seen in 1928 with signs and symptoms of a benign obstructing prostate. A simple perineal enucleation was carried out at that time, and sections made on the tissue removed revealed adenocarcinoma. Within one year, although there were no signs of metastasis, examiners felt that the cancer had extended beyond the capsule of the gland and that total prostatectomy was not indicated. The patient was lost track of until approximately 6 weeks ago when he returned to the dispensary in acute retention. On rectal palpation the prostate was large and nodular. It was judged cancerous and definitely inoperable. Serum acid phosphatase levels were normal and x-rays revealed no evidence of metastasis. A transurethral resection for relief of obstruction was done and sections on this tissue showed adenocarcinoma indistinguishable from that removed 25 years previously. In any series, this would be a 25 year cure, no matter what was done.

A second case is similar. The patient, seen by Dr. Colston in 1941, was believed to have an early operable prostatic cancer. A perineal biopsy revealed a small nodule which on frozen section proved to be adenocarcinoma. A total prostatectomy was done at the same sitting and yet multiple permanent sections failed to reveal any cancer, indicating that the biopsy was generous and had removed the entire cancerous nodule. The patient did exceptionally well until 1951. As a matter of fact, he continues to do well, and yet since 1951 his bones are seen to be riddled with cancer and his serum acid phosphatase is elevated. Endocrine treatment is now being given.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Hot Springs, Va. May 6–8, 1953.

Based on these two cases alone, one might be inclined to think that adenocarcinomas were less malignant than undifferentiated prostatic cancers, and yet a previous attempt at correlating the length of survival with cell types has led me to believe that no significant relation exists and that one cannot predict on the basis of cell type the response to any particular form of therapy

I will be very much interested to hear the follow-up reports to be presented by Dr Baker and by Dr Harrison on the subject of bilateral adrenalectomy for advanced prostatic cancer You will recall their preliminary reports of last year Since last year we have done no more bilateral adrenalectomies As a matter of fact, we have only performed two for prostatic cancer, one surviving a few months and one dying within the last two months, some 15 months after both adrenals were removed Recently, these two cases were presented at the clinical pathological conference held weekly in our Department of Pathology by Dr Arnold Rich One thing in particular interested me Whereas there was definite evidence in certain areas of the prostate that certain cancer cells had undergone atrophy, immediately adjacent to these areas were areas of perfectly good cancer which seemed to be uninfluenced by anything that had been done to the patient Furthermore, sections of untreated prostatic cancer in patients before the days of endocrine management were presented and often showed identical changes I do not mean for a minute to leave you with the impression that I think that prostatic cancer has not been influenced by endocrine manipulations or that further advances will not be made If I thought this, I would discontinue many studies currently in progress involving endocrine relations in prostatic growth I do mean to emphasize, however, that the nature of our controls leaves much to be desired

Recently, in completing a monograph on *The Surgery of the Adrenal Glands* as one of the American Lecture Series in Surgery, I reviewed all the cases of adrenalectomy done to date, not only for prostatic cancer but for cancer of the breast as well Time does not permit review of these data, however, I will read to you the most recent results in a series of 10 patients adrenalectomized for prostatic cancer and reported by the Memorial Hospital group "Three died in the immediate postoperative period, one from cerebral hemorrhage (2 days), one from carcinomatosis (11 days) and one from myocardial infarction (21 days) Six of the remaining seven died within 33 to 294 days after adrenalectomy, two from adrenal insufficiency and four from cancer " The remaining patient was living at the writing of this addendum, his 159th postoperative day Quoting further: "All seven patients had temporary subjective improvement varying from 14 to 210 days, averaging 82 days Only two of the seven had objective improvement lasting 90 and 133 days The most striking beneficial response to adrenalectomy was relief of pain " There has not been a publication from the Huggins laboratory on adrenalectomy for prostatic cancer since that of Huggins and Bergenstal, to be found in *Cancer Research* for 1952, and the results in this series of 7 patients are quite comparable to those of the Memorial Hospital group Of the seven there was one postoperative death, and they judge that three of the remaining six had a clinical remission of the disease of considerable magnitude One patient died of acute pulmonary edema 49 days after adrenalectomy. The remaining four had been observed for periods of 4½ to 9 months at the time of the report. Quoting them: "Perhaps the most striking observation has been the immediate and persistent relief of crippling pain in the bones." In conversation with Dr. Huggins since this report, I have learned that he is performing fewer and fewer bilateral adrenalectomies for prostatic cancer and more and more for cancer of the female breast.

Unfortunately, in most studies to date an insufficient amount of time and effort has been spent in determining the mechanism of action of bilateral adrenalectomy, and it is my feeling that until such is done, little further advance will be made. During the past year there has been further evidence to support the statement which I made at this same meeting in 1952 that cortisone, so necessary in the maintenance of the bilateral adrenalectomized human, is metabolized to androgen. Again this is hard to reconcile with theories which assign improvements following adrenalectomy to androgen withdrawal. Cortisone alone has been as effective at times as adrenalectomy. At present it is my opinion that adrenalectomy for cancer of the prostate and breast is empirical, as Huggins suggests the administration of androgen or estrogen is for advanced breast cancer in the female. If results were better than they are to date, one would be justified in advising this procedure in the individuals hopelessly afflicted with these cancers. In that they are not, it is my belief that these should be considered as research tools and only carried out in institutions equipped for research.

The same holds true for hypophysectomy. One year ago I reported to you on the results in 3 cases of disseminated prostatic cancer subjected to hypophysectomy. Since then, two more cases have been studied. One of these died within a few days after operation, and the other is alive and clinically in fair condition some 6 months after operation. To date total hypophysectomy has not been possible, probably because of the difficulties of exposure, and we are considering ablation of that portion of the pituitary which cannot be removed by radioactive means. In attempting to evaluate the procedure to date, I can simply say that in the two individuals with close to total hypophysectomy, one living 5 months and coming to autopsy and one alive at present, the effects have been comparable to those observed following adrenalectomy. In one whose testes were intact at the time of hypophysectomy, the effects were strikingly like those following castration. We do not recommend the procedure to any of you, but will continue to use it in selected cases in an effort to learn more about this disease.

What the future holds, no one knows, but I am firm in my belief that we will make more progress by carefully studying endocrine effects on prostatic growth in the animal, with careful clinical studies when indicated, than to attempt to draw conclusions from a statistical study of a huge series of patients subjected to any one of a number of endocrine procedures. As I have attempted to point out in an article in the 1952 *Transactions of the Western Section of the American Urological Association* entitled, "What Makes the Prostate Grow," much more must be learned concerning the effects of estrogen withdrawal, estrogen being a secretion of the testis as well as androgen. Much more must be learned of the precise nature of the chemical substances liberated by the testes and by the adrenals. If we were to know more, we could predict with a fair degree of accuracy what analogs or, in other words, closely related steroids, would act as inhibitors of circulating biological gonadal and adrenal steroids. If we were to know more about the effects of the pituitary on benign and malignant prostatic growth, we could design better experiments directed towards chemical inhibition of pituitary action.

The road ahead is long and hard. Someone might make a discovery tomorrow which might put us ahead many years, but I doubt it. I do not think this is a pessimistic attitude but a realistic one. A pessimist would not be in this field. Being a realist, I think that for the immediate future we, as urologists, should make every effort to educate the public and the physician in the early recognition of prostatic cancer, at a time when it is operable and at a time when total prostatectomy in the hands of most offers a 50 per cent chance of 5 year survival without cancer. In the meantime, many of us in our laboratory will endeavor to unravel some of the problems discussed. These largely revolve around the early chemical detection of prostatic cancer, the biological potential of any given tumor, the metabolic action of steroids and the nature and action of competitive steroids.

We have made no progress in the chemical detection of early prostatic cancer, although we are continuing a program of fractionation and identification of urinary steroids hoping to find some one specific for prostatic cancer.

For some time we have considered and have now initiated a program in which we are attempting to correlate survival of human prostatic cancer in the anterior chamber of the guinea pig eye with the degree of malignancy as determined by the clinical course of the disease—a search for the "biological potential."

To date we have been unable to demonstrate any *in vitro* effects of androgens or estrogens on human and animal prostatic slices. We have observed, however, a profound differential *in vivo* inactivation of androgens by the altered liver. This is contrary to our findings using estrogens.

Lastly, a lengthy program is in progress aimed at finding analogs of androgens. In a few years we may have something to report.

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A TRUE HERMAPHRODITE

ARTHUR B. CECIL

Since the founding of this Association in 1886, only 2 cases of true hermaphroditism have been reported before it. These two cases were reported in a paper by Kiefer and McKenna in 1944. The condition of rarity alone, however, would not prompt me to present this subject to you. I have decided to do so because I wish to discuss some original ideas in regard to the surgical treatment of intersexuality.

A. D. 0-7161, aged 6, who had been raised as a boy, was admitted to the Hospital of the Good Samaritan in Los Angeles, California, on December 2, 1935. The case was considered one of male pseudohermaphroditism. The penis showed ventral curvature, below which was a groove running into a urogenital sinus. There was no scrotum, nor could testicles be palpated. At this admission to the hospital a first-stage hypospadias operation was done for straightening of the penis.

The patient was lost sight of for 13 years, and was again admitted to the hospital of the Good Samaritan on August 17, 1948, at which time he was 19 years old (H.G.S. No. B.B. 8080). He had graduated from high school and had lived as a boy. The family history showed that he had four brothers: 24, 22, 17 and 15, and one sister, 21, all living and well and normally formed as were his father and mother.

When patient was 13 years old, and again 5 months previous to this admission, he had had vaginal bleeding. The first time the bleeding lasted for 1 week, and the second time for 3 days. He had male inclinations and desires, but had never had intercourse. He was most insistent that he be constructed as a male. Physical examination showed an individual weighing 140 pounds, 5 feet 6 inches tall. The general contour was that of a female: the breasts fairly large, the nipples highly developed with pigmentation about them. The pubic hair was of female distribution. There was no beard (fig. 1, *A*).

The phallus was 4.5 cm. in length and 2.5 cm. in diameter. The ventral curvature had been cured by the previous operation. There was a dimple representing a glandular meatus. On the ventral surface was a moist area running down to the urogenital sinus. On each side of this groove were labia minora 4 cm. in length (fig. 1, *B*). Just outside of the external ring one could palpate a mass which was about 2.5 cm. in its largest diameter. This was thought to be an undescended testicle. Nothing was made out in the left groin, and no hernia was present on either side. On rectal examination one could palpate a small body which was probably a uterus. A vaginogram showed a capacious vagina and a filling of the uterus and tubes (fig. 2).

On August 28, 1948, I excised the labia minora and did a Thiersch operation for the development of a urethra from the glans penis to the urogenital sinus, leaving the patient to urinate through the urogenital sinus. This operation was entirely successful (fig. 3).

Read at annual meeting, American Association of Genito-Urinary Surgeons, Hot Springs, Va. May 6–8, 1953.

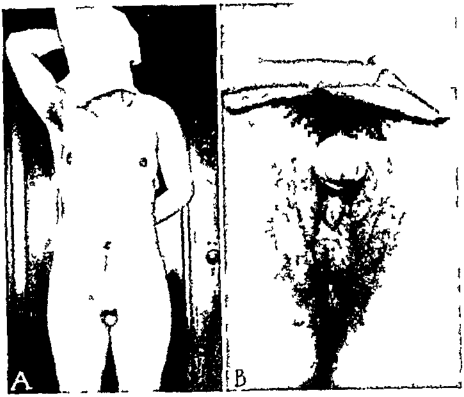

FIG 1

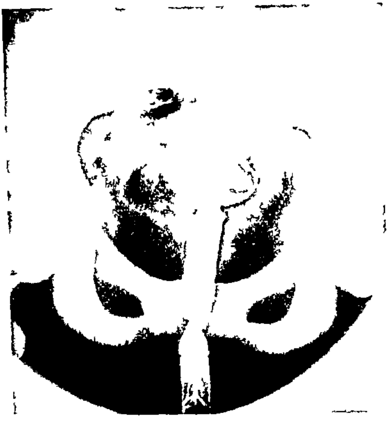

FIG 2

On November 29, 1948, abdominal and right groin exploratory operations were carried out by Dr Kenneth Blake and Dr Arthur Cecil

Total hysterectomy with bilateral oophorectomy and left salpingectomy, exploration of mass in the right groin Upon opening the abdomen the uterus was smaller than one would find in a female 19 years of age On the left side was a cystic ovary which measured 4 cm in diameter Lying above this was the left fallopian tube with its fimbriated end This cystic mass and left tube were removed The right tube was found to extend out into the right inguinal canal, and upon teasing it out with forceps, the fimbriated end was made out, but the tube could not be pulled into the abdominal cavity The uterus was removed just below the cervix After peritonealization, the abdomen was closed An incision

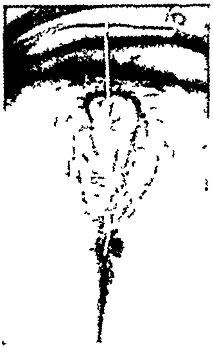

FIG. 3

was now made over the mass in the right groin. The tunica vaginalis was opened, and within it was found a most remarkable organ. A rounded mass 2.5 by 2 cm. was located. The lower pole, which made up half of the mass, was of a grayish color, and the upper pole showed ovarian follicles. There was a definite line of demarcation between these two bodies. Biopsy specimens were taken from both poles and immediately studied by Dr. John Tragerman. The lower pole proved to be a testicle, and the upper pole an ovary. The biopsy opening of the testicle was closed and the ovarian tissue dissected loose from the testicle and removed. The tube was left in because of fear of interfering with the blood supply to the testicle. No attempt was made to change the position of the testicle.

Pathological report (Dr. John Tragerman): "Uterus and cervix are removed together in a slender mass 8.5 by 3.8 by 2 cm. (fig. 4). The fundus is thin and soft showing considerable serosal congestion. The top of the fundus is slightly concave. The cervix is elongated measuring 3 by 2.1 by 1.8 cm. The lower uterine segment is also rather slender. The uterus and cervix are widely opened. The

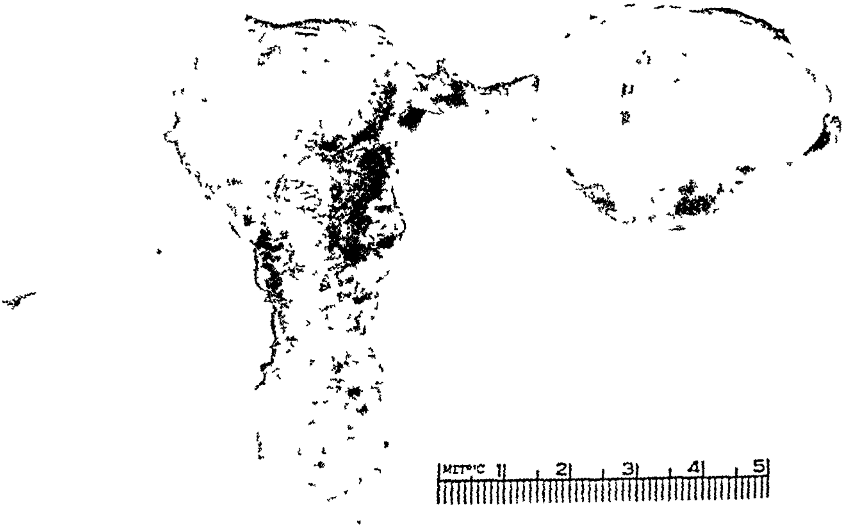

FIG 4

walls vary in thickness. The cervix shows a rather wide canal containing a few transverse corrugations and several mucous cysts. A cord-like band of pale tissue extends from one wall of the internal os upward for about 1.5 cm., and then seems to become incorporated with the endometrium above. The endometrium is less than 1 mm. thick, showing a number of small areas of hemorrhage. The cord-like tissue is nearly 3 mm. in diameter. A block is taken from the uterine wall, at each end of the cord and also from one cornu, where a firm 5 mm. nodule is somewhat suggestive of adenomyoma.

"Microscopic: The uterus shows a rather compact muscle and is lined by a thin irregular endometrium somewhat atrophic in appearance. The nodule in the cornu is suggestive of a small myoma but no glandular structures are present. A block from the internal os shows numerous mucous glands, a few of which are distended. There is also a deeper zone in the tissue containing glands and cysts more like those of the endometrium. The termination of the cord-like structure described grossly shows a projecting nodule of uterine muscle surrounded by a thin inactive layer of endometrium, as already noted. Anatomical diagnosis:—atrophic endometrium. Nabothian cysts of endocervix.

"Left tube and ovary are removed together, the tube measuring 5.5 by .6 mm. The serosa is smooth but quite congested. The tube is slender and tortuous. The distal end is patent. The ovary is a collapsed oval cyst 4.3 by 3.2 by 1 cm. (fig. 4). It has been widely incised through the lower border showing a smooth lined cavity presenting a gray red membrane streaked with congested vessels. A few small yellowish plaques appear in the lining and in the cyst wall. Several flattened follicular cysts of varying size are present in the cyst wall. A block is taken from the wall near the pole.

"Microscopic: The stroma is fairly dense, containing numerous primitive ova, a small follicular cyst and an organizing corpus albicans and a regressing corpus luteum. One field, however, indicates that there are some follicular cysts lining the large cavity. Anatomical diagnosis:—follicular cysts of left ovary.

"Sections A and B are from the right inguinal mass suspected as ovotestis. Section A, from upper pole of right inguinal mass, shows dense ovarian stroma containing numerous primitive ova and part of the lining of a partly collapsed follicular cyst (fig. 5, *A*). Section B shows a group of tubular structures supported by a rather hemorrhagic stroma. Along one surface is a narrow zone of fairly dense fibrous tissue. The cells in the tubules show considerable variation—some are large with granular eosinophilic cytoplasm, others show clear cytoplasm and eccentric nuclei with some tendency to rest near the basement membrane. Other tubules, however, are diffusely filled with similar cells and there is little suggestion of an acinal lumen. The appearance is that of an undeveloped testicle (fig. 5, *B*)."

December 29, 1948, third-stage hypospadias operation, Cecil: Suprapubic drainage was done, and an elliptical incision was made around the opening of the distal urethra and the urogenital sinus. This opening was closed in layers. On the eighth day the suprapubic drainage tube was removed, and at the next urination patient urinated through the urethra in the normal fashion (fig. 6).

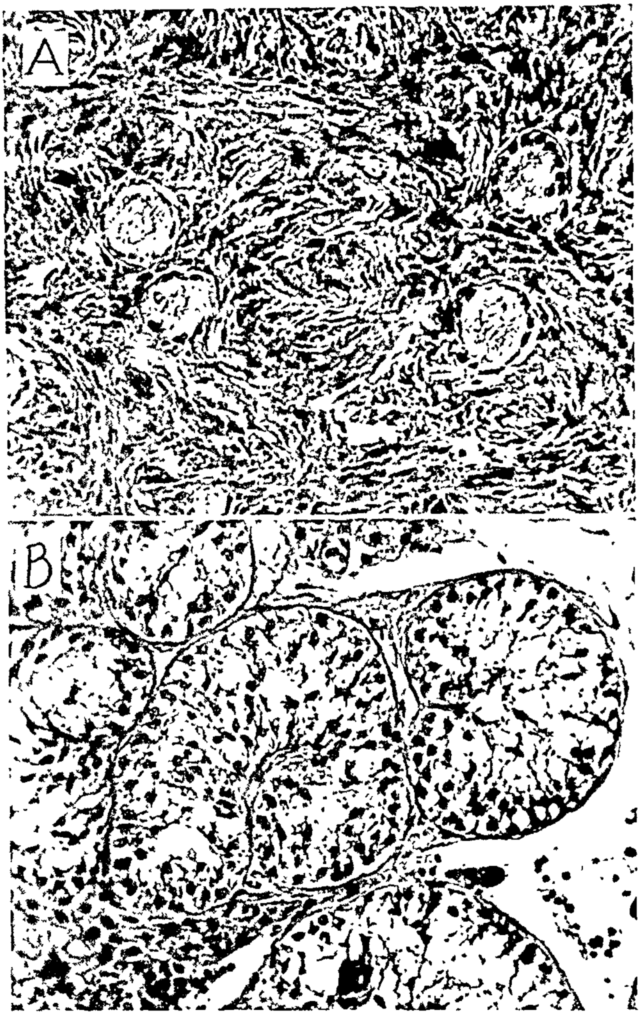

FIG. 5

The final stage in the male construction of this patient was the amputation of the breasts which was done by Dr. Kenneth Blake.

In 1942, Severinghaus[1] reported a study of the chromosomes of an intersex. In this case the secondary sex characteristics were a combination of male and female types. Exploration proved that the patient was a male pseudohermaphrodite. Biopsy specimens of the testicles were studied. The chromosomal content of the cells was found to be normal and the sex chromosomes corresponded with the gonadal sex. No studies of the chromosomal content of a true hermaphrodite have been made. Hooks[2] has given a splendid review of the literature dealing with sex determination, sex differentiation, and the effects of hormones on sex. It would be superfluous to further discuss this subject here.

I shall now take up the treatment of intersexuality which is more particularly in our field of endeavour. I have previously advocated that this treatment should

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[1] Severinghaus, A. E.: Am. J. Anat., **70**: 73–87, 1942.
[2] Hooks, C. A.: J. Urol., **62**: 528–534, 1949.

FIG. 6

begin on the day of the birth of any individual whose sex is in doubt.[3] It is unfortunate that at the present time the only method by which gonadal sex can be determined is by exploration and biopsy of the gonads. As far as determining the gonadal sex is concerned, no cystoscopic, endoscopic or x-ray study is of any value whatsoever. Coffey did uretero-intestinal anastomoses on new-born babies in cases of exstrophy of the bladder. Babies are accustomed to anoxia and stand operation well. There is therefore no reason why an intersex baby should not be explored immediately at birth, and there is every reason why it should be because of the havoc which such an individual brings to a family. If, upon exploration, the baby is found to have ovaries, the clitoris should be amputated at once and the mother told that she has a girl baby. If testicles are found the mother should be told that she has a boy who has hypospadias that can be cured when he is 4 years old. There is no place in the world for an intersex individual. The sensational accounts appearing in the newspapers of today of girls being changed into boys and boys into girls are not tributes to modern medical science but a terrible indictment of the medical profession who did not make this determination when it should have been made: on the day of birth of the individual.

It can be seen from the case which I have presented the tremendous influence of psychic sex. This patient was unquestionably predominantly a gonadal female and, I believe, a genetic female, but because the individual had been raised as a boy, everything else to the contrary, he insisted upon living the life of a boy and being surgically constructed into a male. Psychic sex is something not to wait for but to be developed; all the more important is it that the gonadal sex should be determined at the earliest possible date. I am not, however, advocating the change of psychic sex of an individual on gonadal findings alone later in life.

The case which I have reported brings out an important surgical procedure which I have previously described.[4] In 1949 Howard[5] published an article in which he pointed out the high degree of feminism in cases of hypospadias where the urethra opened in the perineum, and that these cases showed a vagina, uterus and tubes. It occurred to me, therefore, that since I had cured many cases of perineal hypospadias in which a vagina was present but unknown to me, that in the case which I have presented it would not be necessary to remove the vagina as had previously been advocated in such cases. I therefore constructed the terminal urethra as I have described, and anastomosed the urogenital sinus with the urethra. The vagina has given no evidence of its presence. I am therefore convinced that it is surgically proper not to remove the vagina in intersex individuals where male construction is to be carried out.

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[3] Cecil, A. B.: Discussion. Trans. West. Sec. A.U.A., p. 125, 1950.

[4] Cecil, A. B.: J. Urol., 62: 709–712, 1949.

[5] Howard, F. S.. Surg., Gynec. & Obst., 86: 307, 1948.

ADDENDUM

Since presenting this paper, Moore, Graham and Barr have described a method for the detection of chromosomal sex by a skin biopsy (Surg., Gynec. & Obst., **96**: 641, 1953).

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UROLOGICAL PROBLEMS IN AGENESIS OF ABDOMINAL WALL MUSCULATURE

P. PAUL RIPARETTI and DONALD A. CHARNOCK

This paper presents the urological abnormalities associated with agenesis of the musculature of the abdominal wall. Recognition of this syndrome dates back to the turn of the century but it has not been until recent years that improved diagnostic and surgical techniques have made possible the treatment of these patients. Sixty-one cases have been reported, to which we add five.

This syndrome consists of two basic findings: 1) Partial to complete absence of the abdominal wall musculature, 2) abnormalities of the urinary tract, which usually presents enlarged and hypertrophied bladder, hydrourethers and hydronephrosis. Patent urachus, obstructions at the vesical neck and atresia of the urethra have been noted. Other common anomalies are cryptorchidism, malrotation of the intestines, megacolon, spina bifida, pigeon chest and some form of talipes (Eagle and Barrett; Silverman and Haang).

The syndrome occurs predominately in males. Of the cases reported, only three have been observed in females. The mortality rate has been high, most of the deaths occurring in infancy from pneumonia, pyelonephritis, bacteremia and uremia.

Two principal theories have been advanced to explain the pathogenesis of this condition. Osler reported a case in 1901 which he had seen in 1897. In his characteristic way, he had sought the advice of Dr. C. R. Bardeen, then associated with the Department of Anatomy of the Johns Hopkins Hospital. Bardeen suggested that the lack of resistance normally met with in the abdominal wall might allow the bladder to expand rather than to empty secretions into the amniotic cavity. He though this might be due to faulty development of the blood supply.

Stumme in 1903, postulated that obstruction at, or distal to, the bladder neck, early in fetal life, resulted in dilatation of the bladder and involvement of the ureters and kidneys. The enlarging urinary system caused atrophy of the abdominal wall musculature, either by direct pressure or by diminishing its blood

In our opinion, the theory of Stumme is the more logical, but neither theory adequately explains the problem. While over half the cases reported had bladder neck obstruction, several, including two of our own, showed obstruction at a higher level. Moreover, many infants with dilated bladders due to bladder neck obstruction have no abnormality of the abdominal musculature.

The diagnosis of this syndrome usually does not present any great problem. The condition is readily recognized by the obstetrician oı the pediatrician. Upon examination of the infant, the abdominal skin is usually wrinkled and looks like the skin of a dried prune. The underlying abdominal viscera may easily be seen beneath the skin of the thin abdominal wall and the various organs readily palpated. If the infant is placed on his side the abdominal viscera fall to the dependent portion and if placed flat on his back, the flanks bulge. As most of these cases are males, bilateral cryptorchidism is usually present.

Read at annual meeting, Western Section of American Urological Association, San Francisco, April 27-30, 1953.

In studying these unfortunate infants a thorough urological examination is imperative. A nonprotein nitrogen determination is obtained which serves as a base line for future comparison of the patient's progress. The residual urine should be determined and a cystogram done. We prefer the delayed cystograms as described by Stewart since a reflux up the ureters may outline the upper tract, thereby eliminating the necessity of retrograde examination (Stumme). Cystoscopy should be done early and one must search the bladder neck very carefully for any evidence of obstruction in this suspected area. If the nonprotein nitrogen is within reasonable limits, excretory urography using delayed 1, 2 and 3 hour films is valuable. Some of our best urograms were made 3 hours after the intravenous injection of the iodide solution. It goes without saying, that the pediatrician and the urologist should work together in the treatment of these infants.

CASE REPORTS

Case 1: Baby P.M., aged 3 weeks, was admitted to the Childrens Hospital on September 28, 1948. The infant was a full term baby, weighing 7 pounds, 5 ounces at birth. No complications occurred during delivery and no prenatal complications developed. At birth, the obstetrician noted the absence of the anterior abdominal wall musculature.

Examination of the abdomen revealed bulging of the flanks (fig. 1, *A*). The intestinal pattern could easily be seen beneath the anterior abdominal wall. No abdominal muscles were palpated. The bladder was firm and distended. Bilateral cryptorchidism was present.

The hemoglobin was 141 per cent. The white blood cell count was 21,900. The urine showed 1 to 2 plus albumin and was loaded with white blood cells. The nonprotein nitrogen was 65 mg. per cent and rose to 160 mg. per cent. The CO_2 combining power was 17 volumes per cent. A cystogram revealed bilateral hydro-urether (fig. 1, *B*). A No. 6 ureteral catheter was passed into the bladder and 10 cc of cloudy urine obtained. The bladder remained distended.

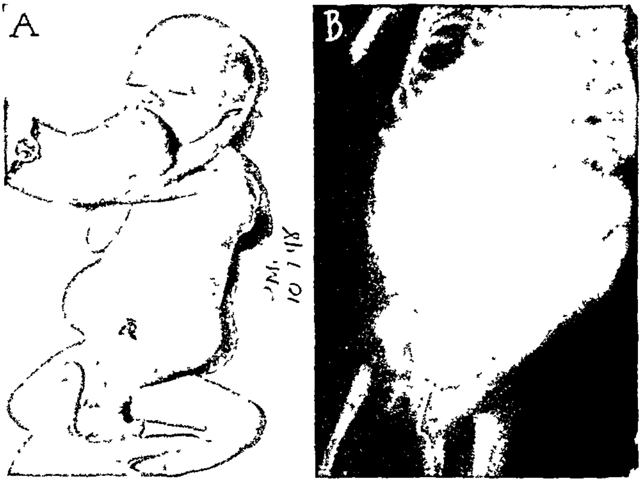

FIG. 1. Case 1. *A*, note bulging of flanks and distended bladder. *B*, delayed cystogram showing dilated ureters.

The baby did poorly from the onset, refusing his formula and vomiting. Dehydration progressed and acidosis increased. The nonprotein nitrogen continued to rise and the infant expired on October 14, 1948.

Autopsy findings were confined to the abdominal wall and genito-urinary systems. There was no evidence of muscles in the ordinary sense of the word. A few fibers of the internal and the external oblique were seen. No recti fibers were found. The abdominal organs were in their normal anatomical position. The right kidney weighed 5 gm. and the left kidney 10 gm. The pelves were dilated and contained a large amount of thick yellow fluid. There was an extreme thinning of the cortex. The pelvic mucosa was thickened and injected. On the right side, an obstruction was found in the ureter about 1 cm. proximal to the bladder and consisted of a fibrous thickening for a distance of 2 mm. The left ureter was tremendously hypertrophied, measuring 1 cm. in thickness and was very firm. There was marked thickening of the bladder wall. The mucosa of the bladder appeared to have minimal trabeculations. No bladder neck obstruction was apparent. On opening the urethra, no obstruction was noted. The right testicle was felt along the course of the right ureter and the left testicle was not located.

Microscopic findings of the kidneys showed the tubules and the glomeruli to be destroyed and in many places replaced by connective tissue. Clumps of bacteria were seen in the tubules. The ureters showed thickened fibrous walls. The bladder wall musculature showed thickening with increase in the size and the number of fibers.

Case 2. Baby S. R., aged 2 weeks, was admitted to the Childrens Hospital on April 14, 1949. Birth weight was 7 pounds, 10 ounces. The baby was said to have been strong and healthy at birth, but on the third day he became feverish and refused to eat. The parents were told at the time of birth of the abdominal wall abnormality and the possibility of associated genito-urinary abnormalities.

Physical examination revealed a small, malnourished infant in severe dehydration with complete absence of the anterior abdominal wall musculature and with marked wrinkling of the anterior abdominal skin. The kidneys were palpable in their normal position. There was bilateral cryptorchidism and a moderate degree of phimosis.

Laboratory results showed a hemoglobin of 16.6 gm. and a white blood cell count of 34,400. The nonprotein nitrogen was 91 mg. per cent and it rose to 122 mg. per cent a few days later. A blood Kahn and Kline were negative. Several urine examinations were done and all showed 4 plus albumin and were loaded with white blood cells. Culture of the urine revealed hemolytic staphylococcus aureus.

Nos. 10 and 12 sounds were passed through the urethra with some difficulty. It was felt at that time that there was a bladder neck obstruction or that there was a valve in the posterior urethra. Cystogram revealed bilateral hydro-ureter and enlarged smooth bladder. The infant did poorly, failed to respond to antibiotics and died on the sixteenth hospital day.

Autopsy showed a complete absence of the musculature of the anterior abdominal wall. The skin was thrown into wrinkles and folds. The intestinal pattern and shape of the various underlying organs was outlined against the skin of the abdomen. All of the abdominal organs were easily palpated. The right kidney weighed 35 gm. Both kidneys showed a moderate amount of fetal lobulation. The left kidney was markedly hypoplastic. Upon opening the kidneys the calyces were found to be filled with infected urine. There was a marked degree of hydronephrosis. Both ureters were markedly dilated and tortuous throughout their entire course and resembled small bowel in gross appearance. No apparent obstruction was found at the ureterovesical or the ureteropelvic juncture. The bladder wall was thickened but there was no evidence of sacculation or trabeculation. Both testes were found at the pelvic brim. No bladder neck or urethral obstruction was detected.

Case 3. Baby M. N., aged 36 hours, was admitted to the Childrens Hospital on February 2, 1950. The obstetrician noted a complete absence of the anterior abdominal musculature and the infant was sent to this hospital for urologic evaluation.

Physical examination demonstrated a flaring-out of the lower thoracic cage (fig. 2, *A*). The abdomen showed marked wrinkling of the anterior abdominal wall and there was complete absence of the musculature in this area. There was a patent urachus located approximately 2 cm. below the umbilicus in the midline. Urine was draining from this area. The bladder could be percussed up to this point. The abdominal organs could easily be felt through the abdominal wall. Both kidneys were palpable. Bilateral clubbed feet were present.

Laboratory results showed a hemoglobin of 23.6 gm., 152 per cent. Platelets were normal. The white blood cell count was 11,400. The urine showed 4 plus albumin with many white blood cells. The nonprotein nitrogen on admission, was 48 mg. per cent.

The color was good. The respirations were normal and the infant was quite active. Some urine was seen to come out of the penis but most of the time the urine drained from the patent urachus. A No. 5 ureteral catheter was easily introduced into the orifice of the patent urachus and a cystogram was done (fig. 2,

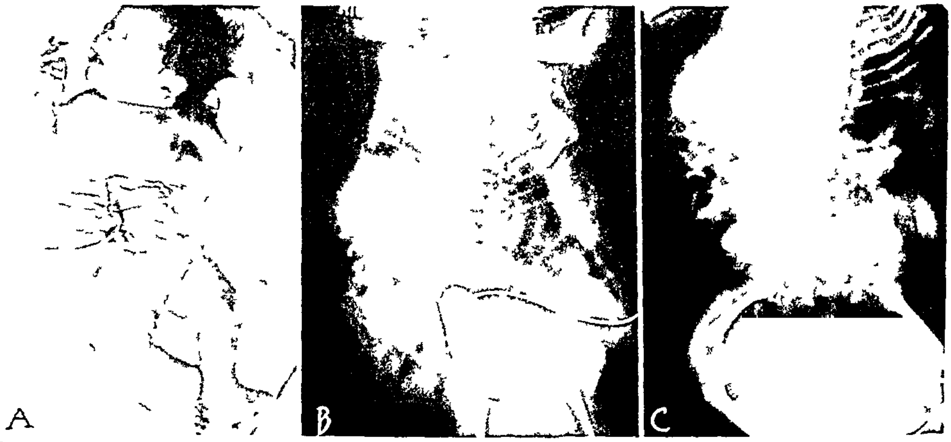

FIG 2 Case 3. *A*, wrinkling of abdomen and deformity of feet *B*, cystogram done through patent urachus with No 6 ureteral catheter Note deformity of rib cage. *C*, 3 hour delayed excretory urogram, showing dilated ureters.

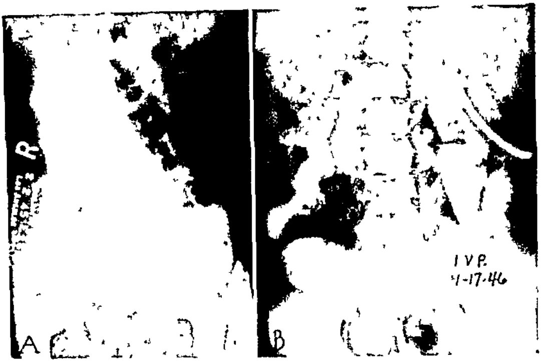

FIG. 3. Case 4. A, cystogram showing marked deformity of bladder. B, bilateral nephrostomy and urethral catheter. Dilated and angulated ureters.

B). The bladder outline indicated enlarged hypertrophied bladder with a rather smooth wall. There was no reflux of the dye into the ureters and the kidneys. On February 12, 1950, an excretory urogram was done. Prompt excretion of the dye occurred in both kidney pelves and in the right ureter. In the 2-hour film, both ureters an both kidneys were well visualized. The ureters were extremely tortuous and the pelves were markedly dilated. The calyces were not outlined (fig. 2, *C*).

A suprapubic cystotomy was done and the infant was discharged and has been followed in the clinic. His general condition is good.

Case 4. R. H., aged 17 years, was first admitted to the Childrens Hospital at the age of 12 years. The past history revealed that he was another example of agenesis of the anterior wall musculature with urinary tract abnormalities. He had his first attack of pyuria in 1937. He was treated with sulfa drugs available at that time and his symptoms disappeared. An abdominal support was fitted which he has worn faithfully since then. He had recurrences of chills, fever, and pyuria during the intervening years.

On physical examination the chief findings were related to the abdominal wall and genito-urinary systems. Complete agenesis of the anterior abdominal muscles was present; the bladder could be palpated up to the umbilicus. Neither kidney could be felt. The testicles were not in the scrotum. A catheter was passed into the bladder without undue difficulty and purulent urine was obtained.

Laboratory tests showed a hemoglobin of 81 per cent, white blood cell count of 16,000, the nonprotein nitrogen was 31 mg. per cent, and the urine showed 1 plus albumin with many white blood cells. The urine culture produced E. coli. Cystogram reveled a smooth, large bladder (fig. 3, *A*). An excretory urogram revealed bilateral hydro-ureter and hydronephrosis (fig. 3, *B*). In February 1945, cystoscopy showed no evidence of bladder neck obstruction or valve formation. The ureteral orifices could not be localized due to the generalized inflammation of the bladder wall. A urethral catheter was left in place for drainage. In March, 1945, a left nephrostomy was performed. The kidney showed hydro-ureter and hydronephrosis with marked thinning of the kidney parenchyma. On May 1945, a right nephrostomy was done. In each of the incisions only an occasional fiber of the internal and the external oblique were encountered. In 1947, the left ureter was explored and was re-implanted into the bladder for better drainage. At the time of the left partial ureterectomy and re-implantation of the ureter into the bladder a cystotomy was also done. At the present time his bladder is quite decompensated. He is being maintained on cystotomy drainage. Both nephrostomy tubes have been removed. He wears an abdominal support and carries on routine activities. The general mental and physical condition of this boy has been satisfactory. He is now 20 years old and is attending college.

Case 5. M. S., aged 3½ years, a Negro, has had multiple hospital admissions at the Santa Barbara County and the Cottage Hospitals, for upper respiratory and urinary tract infections. At birth it was noted that he had agenesis of the abdominal wall musculature and the parents were told of the possibility of genito-urinary disease. He began to walk at 18 months and has worn an abdominal corset since 1 year of age. On physical examination, the chief findings were a prominence of the bony sternum with a depressed ensiform process (fig. 4, *B* and *C*). Partial to complete absence of the anterior abdominal wall musculature was present and prolapse of the abdominal contents. During his many hospital admissions, his urine has shown infection. The nonprotein nitrogen has varied from normal to 60 mg. per cent. He has bilateral cryptorchidism.

In April 1952, excretory urography disclosed some dye in the left kidney region, but no dye was in either kidneys, ureters, or bladder (fig. 4, *A*). In August 1952, retrograde pyelograms were done. A No. 16 Brown-Burger cystoscope was used to visualize the bladder which was seen to be smooth, without trabeculation, and both ureteral orifices were patulous. The bladder neck was carefully visualized

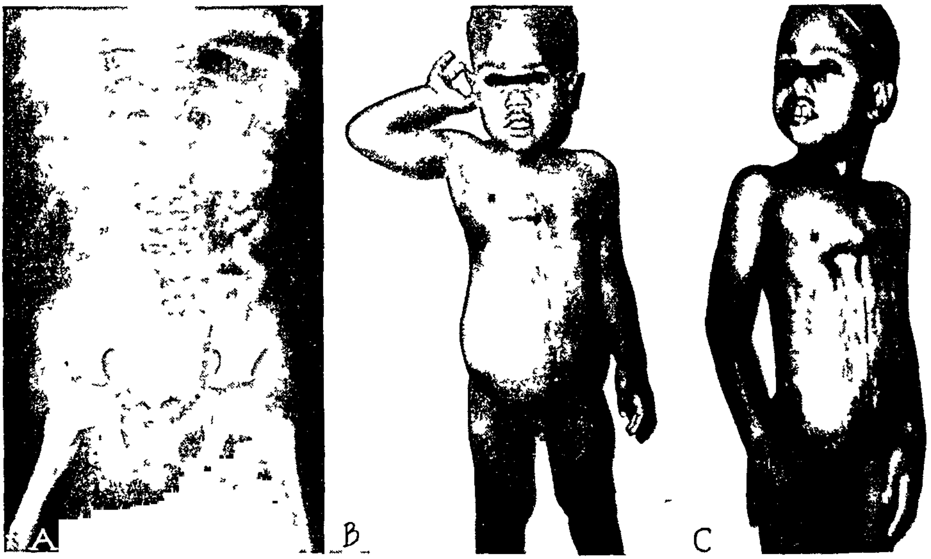

FIG. 4. Case 5 *A*, delayed cystogram showing reflux of dye and hydro-ureters and hydronephrosis. *B*, first operative procedure. Note bulging of right abdomen. *C*, postoperative condition. Illustrates improved abdominal support. (Photographs in *B* and *C*, courtesy of Dr Kathryn L. Stephenson.)

and there was no evidence of obstruction in this area. The residual urine was checked at various times. This varied from 0 to 100 cc.

A plastic surgeon, Dr. Kathryn L. Stephenson, became interested in the patient and it was decided that a different approach should be taken to try to correct the genito-urinary changes. Three operative procedures were undertaken to strengthen the abdominal walls. At the first operation a thin graft was taken from the abdomen with a dermatome. It was elliptical in shape and extended from the pubis to sternum. The adjacent skin and subcutaneous issues were undermined and superimposed to the midline. At the second operation, this procedure was repeated more laterally on the right and also on the left side. Following thickening of the abdominal wall, additional support was given in a third operation by the use of homogenous fascial transplants from the ribs to iliac crest, from the pubis to the sternum and from the iliac crest to the ribs on the opposite side.

The purpose of the grafts were twofold; to facilitate defecation and urination and to prevent the increasing chest deformity by counter traction on the rib cage. Between operations he wears abdominal support, is up and around and is in fairly good health. His urine, at times, is infected. This is controlled with specific antibiotic therapy. He voids with a fairly good stream. It is too early to evaluate this interesting approach to the problem but further follow-up will be forthcoming. This case may give an index of the role of the abdominal musculature in the emptying of the bladder.

The treatment of these cases will tax the ingenuity of the urological surgeon. In general it may be divided into three phases: 1) obtaining adequate urinary drainage; 2) specific antibiotic therapy; 3) abdominal support.

It is of primary importance to obtain adequate urinary drainage in order that the kidney parenchyma may be conserved. The methods for obtaining this varies with each patient and there is no stereotyped treatment for any of these cases. Each must be treated as an individual. Each case needs adequate urological work-up.

The surgical attack on the bladder neck to relieve bladder neck obstruction, as described by Greene, is a recognized method of obtaining adequate drainage and this should be done in all cases where bladder neck obstruction is found or even suspected. This may be done transurethrally, as advocated by Nesbit and by Emmett, or by the retropubic approach, as described by Burns and by Young. Depending upon the particular situation, as demonstrated by excretory and retrograde pyelograms, the ureterovesical or ureteropelvic juncture may have to be treated. Emergency nephrostomy may be necessary to get the infant into proper condition for further surgical procedures. It must be remembered that each case is an individual problem and should be handled as such.

It is important to support the abdomen of these children. This not only gives them a sense of safety but it facilitates urination and defecation. Abdominal corsets of various types may be used.

The treatment of the urinary tract infection is important and specific treatment should be given to these patients.

The approach to the problem by an attempt to make an anterior abdominal the presence of an obstructive lesion or a urinary tract calculus had been excluded. Cultures of the urine were obtained in 40 cases prior to starting therapy. The urine culture was inadvertently omitted in 10 cases, but they were included in the study because of the evidence of bacterial infection that was present in the stained sediment. Although the specific effect of Furadantin could not be determined in this group of patients, they were evaluated from the standpoint of changes produced in the bacterial content of the urinary sediment as well as symptomatic improvement. The results of this study were divided into the following three groups: Laboratory cures, clinical improvement and failures. The laboratory cures were determined on the basis of negative cultures or an absence of bacteria and leukocytes on the gram stained urinary sediment. The cases that were considered clinically improved were free of symptoms of urinary infection, but the urine contained bacteria and leukocytes. The patients who continued to have symptoms and show laboratory evidence of urinary infection were designated as failures after 14 days of treatment with Furadantin.

Table 1 shows the type of micro-organisms found in the urine of the 50 patients included in this study and the response of these organisms to Furadantin. Until specific identification of the coliform bacilli was requested, the laboratory reported Escherichia coli, intermediate coliform, and Aerobacter aerogenes as coliforms. A laboratory cure was obtained in eight of the ten cases in this group identified as coliform bacilli. In the remaining 21 cases, 11 of the 14 cases of E. coli and three of the 5 cases of Aerobacter aerogenes responded well to Furadantin. The 2 cases of intermediate coliform bacilli were resistant to Furadantin. There were 3 cases of mixed infections. In two of these cases the mixed infection was caused by Proteus organisms and Streptococcus fecalis and in one case by Pseudomonas and Micrococcus pyogenes. Although no laboratory cures were obtained in this group, two of the 3 cases showed clinical improvement. In 10 cases the organism was identified as either a gram negative bacillus

TABLE 1. *Micro-organisms treated with Furadantin*

ORGANISM	NUMBER OF CASES	LABORATORY CURE	
		Yes	No
Escherichia coli	14	11	3
* Coliform	10	8	2
Intermediate coliform	2	0	2
Aerobacter aerogenes	5	3	2
Pseudomonas aeruginosa	3	1	2
Gram negative bacilli	9	4	5
Gram positive cocci	1	1	0
Proteus vulgaris and Streptococcus fecalis	2	0	2
Pseudomonas aeruginosa with Micrococcus pyogenes	1	0	1
Amicrobic pyuria	3	2	1
Totals	50	30	20

* Coliform includes E. coli, Aerobacter aerogenes, and intermediate coliforms.

or a gram positive coccus. A laboratory cure was obtained in 5 of the 10 cases. A negative culture was obtained after treatment in one of the 3 cases of Pseudomonas aeruginosa. Three cases of amicrobic pyuria were included in this study and in 2 cases the urine was free of pus cells after a course of treatment with Furadantin. Nineteen of the patients used in this study had chronic infections of the urinary tract and had been unsuccessfully treated with sulfonamides and antibiotic agents. Furadantin effected a laboratory cure in six of these patients and clinical improvement in five when under active treatment.

TOXICITY

Eight patients experienced nausea and two vomited while receiving Furadantin. It was necessary to discontinue the drug in 4 patients. In the remaining 6 cases, the nausea subsided after instructing the patients to take the medication after meals. There were no instances of allergic skin reactions or anemia noted in the entire group of patients treated with Furadantin.

CONCLUSION

Furadantin is an effective drug in the treatment of urinary infection caused by Escherichia coli and Aerobacter aerogenes. It may be useful in patients who have manifested allergic reactions to the sulfonamides and in instances where antibiotics have not successfully controlled the infection. Several patients experienced clinical improvement while receiving Furadantin, although the urine cultures continued to show the presence of bacteria. Furadantin was found to be ineffective in mixed infections. We could not evaluate the effectiveness of Furadantin in cases of urinary infection caused by Proteus vulgaris based upon its use in 2 cases, but other investigators have found it to be an effective agent against this micro-organism. While this series is small and does not contain an adequate representation of the type of bacteria found in urinary tract infections, it is our impression that Furadantin is a valuable adjunct to the already available chemotherapeutic and antibiotic agents. We are aware of the shortcomings in the method by which this study was carried out from a laboratory standpoint. However, the results obtained enabled us to gain a general clinical impression of the effectiveness of Furadantin which in turn should encourage more detailed studies.

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THIOSULFIL IN URINARY TRACT INFECTION

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For the treatment of urinary tract infections, a new member of the sulfonamide family is available to the American medical profession. This drug has been used extensively in Europe for the last 12 years[1, 2, 3, 4, 5, 6, 7, 8] and in the past year it has found wide acceptance in Canada.

Its chemical, pharmacological and antibacteriological properties, when compared with other sulfa drugs now in use, merit serious consideration.

Of major interest are comparisons of 1) percentage of acetylation, 2) solubility in urine in a wide Ph range, 3) incidence of systemic reaction, 4) rates of absorption from the intestine and excretion by the kidneys and 5) antibacterial spectrum and effect.

The structural formula is depicted in figure 1.

The low acetylation is probably related to the stability of the drug with strong bonding of the H atoms. The location and availability of the N radicals effects its chemical behavior. See figure 2. When giving a sulfa drug the liver converts a portion of the drug by adding the $Ch_3C=O$. In effect the blood stream contains two drugs with differing properties, the undesirable reactions caused by the acetylated form.

There are variations in the degree to which different sulfonamides are acetylated as well as individual variations in acetylation of a given sulfonamide (fig. 3). The ranges of acetylation are shown as reported.[9]

Comparative solutility in the urine of the unacetylated forms is charted in figure 4.[9, 10]

Comparative solubilities in the urine of the acetylated forms are charted in figure 5. [9, 10]

Figure 6 depicts the incidence of hematuria after the administration of various sulfonamides. The low incidence of hematuria on the administration of Thiosulfil is probably related to the high solubility of both the acetylated and unacetylated forms with the practical absence of crystaluria even in the presence of restricted fluid intake.[11, 12]

Thiosulfil is seen to be rapidly absorbed and excreted, proper blood levels may be obtained by appropriate dosage (fig. 7.).[9, 11]

Figure 8 depicts inhibition of growth of Ps. aeruginosa in vitro in urine with varying concentrations of various sulfonamides.[10]

Read at annual meeting, Western Section of American Urological Association, San Francisco, April 27-30, 1953.

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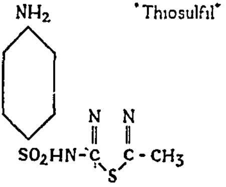
The inhibition of growth of P. vulgaris in vitro in urine with varying concentration of various sulfonamides is charted in figure 9.

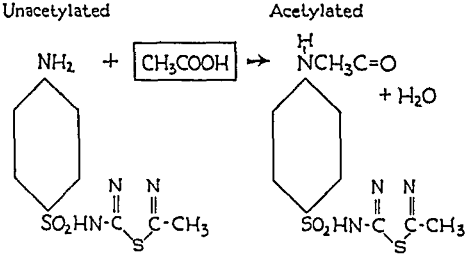
Clinical use during the past year has consisted of the treatment of 100 patients with urinary tract infection. No unpleasant or harmful reactions were encountered.

Nine patients (with urinary tract infection) who were sensitive to all other



2-Sulfanilamido-5-methyl-1,3,4 thiodiazole
(Europe 'Lucosil', 'Urolucosil')

FIG. 1



Solubility in H_2O at pH 7:

THIOSULFIL 978 gm/100cc
SULFADIAZINE 0 04 gm "

FIG 2

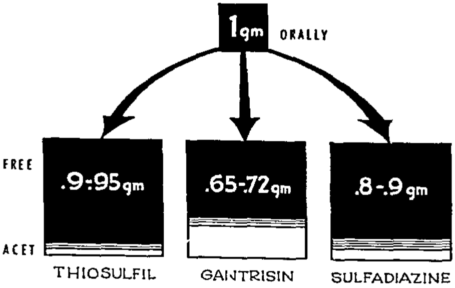


FIG. 3

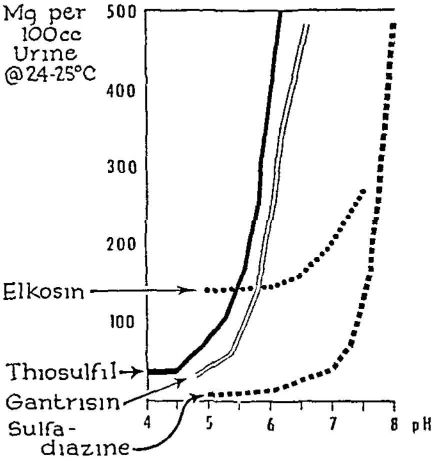


FIG. 4

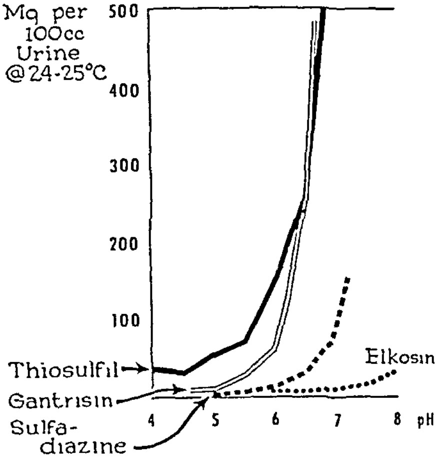
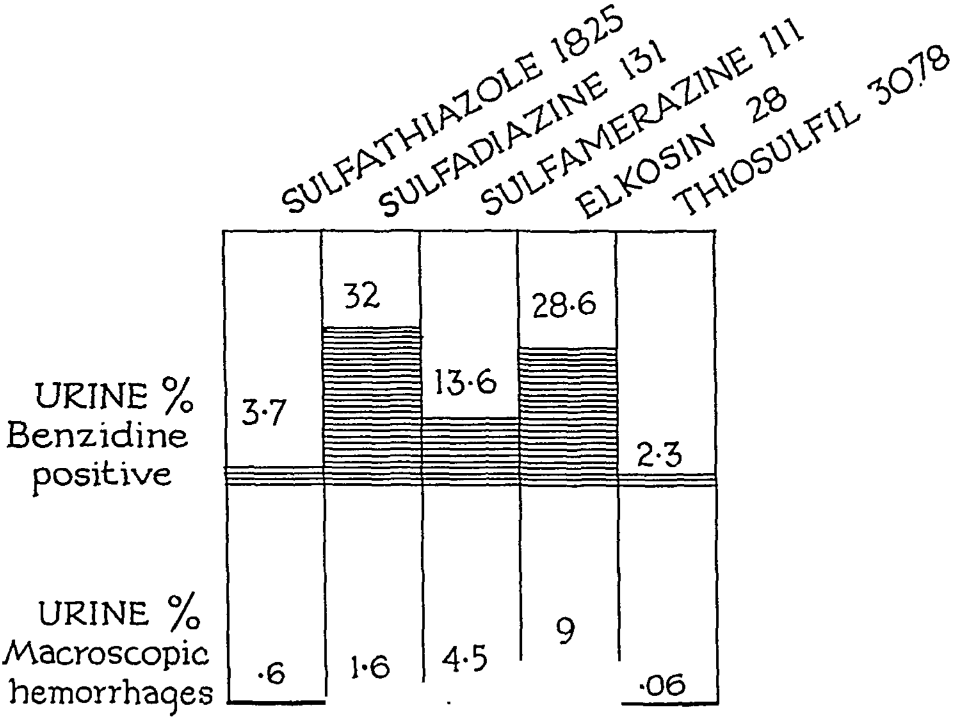


FIG. 5

sulfonamides, some in severe degree, all tolerated therapeutic doses of Thiosulfil with cure of their infection.

Thirty-one patients with mixed infections, many of whose infections had refused to respond to various sulfa drugs and antibiotics and who on complete genito-urinary survey. including cystoscopy and pyelography, demonstrated no genito-urinary anomaly, were studied. In this series a cure rate of 70 per cent



Nissen et al
1950

FIG. 6

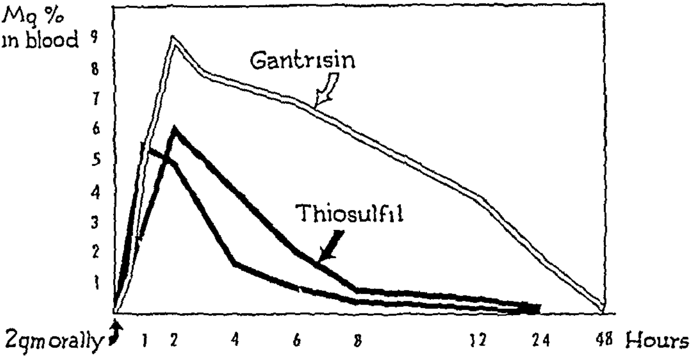
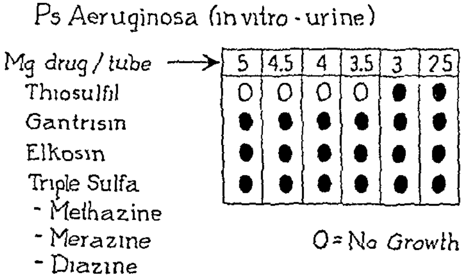


FIG. 7

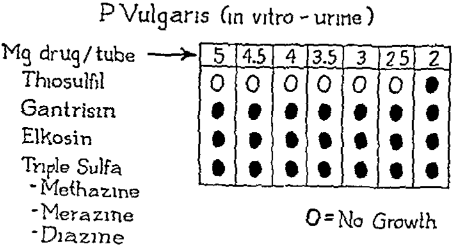


Ps Aeruginosa (in vitro - urine)

Mg drug / tube →	5	4.5	4	3.5	3	25
Thiosulfil	O	O	O	O	●	●
Gantrisin	●	●	●	●	●	●
Elkosin	●	●	●	●	●	●
Triple Sulfa - Methazine - Merazine - Diazine	●	●	●	●	●	●

O = No Growth

FIG. 8



P Vulgaris (in vitro - urine)

Mg drug / tube →	5	4.5	4	3.5	3	25	2
Thiosulfil	O	O	O	O	O	O	●
Gantrisin	●	●	●	●	●	●	●
Elkosin	●	●	●	●	●	●	●
Triple Sulfa -Methazine -Merazine -Diazine	●	●	●	●	●	●	●

O = No Growth

FIG. 9

was obtained, 4 per cent showed no improvement and 26 per cent showed moderate to marked improvement.

Mrs. S. H. aged 24, a nurse, was seen on May 25, 1953 in consultation complaining of hematuria with severe right renal and abdominal pain requiring morphine for relief. Excretory urograms demonstrated right hydronephrosis with decreased kidney function and right ureteropelvic junction obstruction. Her temperature was 101.8F. The urine contained many white blood cells and red blood cells. On gram stain the urine contained short gram negative bacilli. The patient had been under treatment for the previous 3 months with rather poor results inasmuch she was found to be sensitive to all sulfa drugs and most of the antibiotics.

Thiosulfil, .5 gm. was given every 4 hours. In 36 hours the temperature was normal with no evidence of drug sensitivity and the patient was free of pain. In 10 days urine studies were negative. Split renal studies and retrograde pyelograms demonstrated marked recovery of right kidney function.

SUMMARY

A new member of the sulfonamide family is available. I have studied its use in Europe with increasing interest in the past 3 years and have had the opportunity to give it 1 year's controlled clinical trial. Its chemical, pharmacological and antibacteriological properties are compared to other members of the sulfonamide family in present favor.

Clinical trial appears to indicate that the drug can be tolerated where other sulfa drugs cannot and that it is effective where some others are not. An attempt has been made to discover and explain why this is true.

CONCLUSION

Thiosulfil has an extremely low rate of acetylation.

It is highly soluble in urine over a wide Ph range in both the unacetylated and acetylated form.

There is a low incidence of systemic reaction.

The rate of absorption from the intestine and excretion by the kidneys is high.

It has an antibacterial spectrum and effect which compares favorably with other members of the sulfa family.

I believe that Thiosulfil deserves wide clinical acceptance.

ADDENDUM

During the year since this study was reported, additional clinical information has been obtained. Thiosulfil has now been under trial and observation in my practice for 30 months.

It has been necessary to interrupt treatment because of mild sensitivity consisting of loss of appetite and lassitude in one case in a series of 300 patients.

I do not hesitate to give Thiosulfil to a patient in whom there is a history of sensitivity to sulfa drugs. I have seen no cases of exanthemata, urticaria, emesis, fever, hematuria or crystaluria.

The drug has been given with good results in the presence of urinary retention and severe uremia. At my suggestion it was given with good results to control a secondarily infected eczema on the hands of a 7-year old boy with severe, acute nephritis and sensitivity to antibiotics.

Early experiments in rats indicate that large amounts of Thiosulfil can be placed in the abdominal cavity without subsequent evidence of peritoneal irritation; 50 mg. were placed in the abdominal cavity of rats weighing 180 gm., the equivalent of 25 gm. in the abdomen of a man weighing 90 kilograms.

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RESULTS IN ARTIFICIAL INSEMINATION

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Contrary to usual belief, human artificial insemination has been practiced in the United States for nearly 100 years and its use is steadily increasing

The first inseminations in this country were performed by J Marion Sims[1] in 1866, who inseminated six women artificially a total of 55 times, with one resulting pregnancy, which terminated in a spontaneous abortion

In the ensuing years, very little insemination was attempted, Rohleder,[2] in 1924, was only able to collect 127 cases with 52 pregnancies Engleman,[3] in 1928, brought the series up to 185 cases with 65 pregnancies

This report will consist of a comparison of results of AID using two different methods of insemination

With the first method, the semen is instilled onto the cervix with a Cary cannula The second method uses a relatively tight-fitting plastic cup, first described by Whitelaw [4]

In either case, the indications for performing AID remain the same 1) The husband must be irreparably sterile 2) The wife's pelvic organs must be normal 3) The wife must have normally functioning tubes 4) She must ovulate normally in a majority of her cycles 5) Both husband and wife must equally desire this method of reproduction and both must understand the possible legal and psychological consequences

I believe that again the prerequisites for insemination should be reviewed They are as follows

1) Both wife and husband should be interviewed and the infertility of the husband determined

2) The probable fertility of the wife must be determined

3) There should be a "cooling off" period, an interval during which the couple can review the picture dispassionately and during which the physician will see both husband and wife and familiarize himself with the mental and psychological make up of the couple

4) A careful selection of the donor is paramount The donor must remain anonymous, and should never be a relative or friend of husband or wife The donor must be fertile, above average mentally and physically, with no hereditary diseases He should resemble the husband as closely as possible, racially and physically and have an Rh factor compatible with that of the wife

5) The specimens of semen should be obtained and delivered to the office as

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Read at annual meeting, Western Section of American Urological Association, San Francisco, April 27–30, 1953

[1] Sims, J M Clinical Notes on Uterine Surgery, With Special Reference to the Management of the Sterile Condition New York William Wood & Co , 1866

[2] Rohleder, H Normale, Pathologische und Kunstliche Befruchtung beim Menchen Berlin, 1924, p 204

[3] Englemann, F Klin Wehnschr 7 1563 1928

[4] Whitelaw, M J Use of the cervical cap to increase fertility in cases of oligozoospermia Fert & Steril , 1 33–39, 1950

TABLE 1

	TOTAL NUMBER	INSEMINATIONS OLD METHOD		INSEMINATIONS NEW METHOD (PLASTIC CUP)	
Cases	177	50		127	
Pregnancies	134	28		106	
% Pregnancies	75.7%	56%		83.3%	
Full-term deliveries	84				
		Preg	Not Preg	Preg	Not Preg
Inseminations	1199	213	226	567	193
Average No. Inseminations	6.81	7.6	10.28	5.34	9.19
Cycles	677	104	109	349	115
Average No Cycles	3 82	3.71	4.95	3.29	5.47

soon as possible and in such a manner as to insure no possible meeting between donor and recipient.

6) A written consent to the insemination, signed by both husband and wife, before a witness, is essential.

The timing of the insemination is based on the patient's previous menstrual records and on her basal body temperature readings. The attempt is made to inseminate on the drop in temperature, this being 14–15 days before the shortest expected period that the patient has recorded. Further inseminations are then performed, if necessary, on alternate days during the mid-cycle or on any other drop in temperature.

The new technique of performing artificial insemination is very simple. The cervix and vagina are first cleaned and dried by wiping with a cotton pledget. On the first inseminations, cervical mucus is removed for study and a sperm penetration test performed.

The semen is then placed in a plastic cup of correct size, and inserted into the vagina and over the cervix, where suction holds the cup in place. Care must be taken that none of the semen is spilled during insertion of the cup. The cup is slipped along the posterior wall of the vagina in a horizontal position, dome down, until the cervix is reached, where a slight added pressure posteriorly permits the cup to slip over the cervix. Thus the cup acts as a means of keeping the entire semen specimen in close contact with the cervical os. It is left here for 24–48 hours, when it is removed either in the office by the physician or by the patient at home. If removed in the office, an examination of the cervical mucus is done and usually myriads of active sperm are found, even though up to 48 hours have elapsed since the insertion of the semen.

In the total series, 177 women were inseminated with the semen of a selected donor, resulting in 134 pregnancies (75.7 per cent).

In the first group of 50 cases, where the Cary cannula was used, a total of 28 patients became pregnant (56 per cent). These include 36 previously reported by me[5] in 1946, plus 14 subsequent cases.

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[5] Haman, J. O.: Artificial insemination. Calif. Med., **68**: 353, 1948. No. 5, May, 1948

TABLE 2

Pregnancies		
Male	51	(60.71%)
Female	33	(39.29%)
Unknown	4	
Miscarried	24	(17.9%)
Undelivered	22	
No pregnancies	43	
Total	177	

The second group of 127 cases, in which the plastic cup was used, resulted in 106 pregnancies (83.3 per cent) (table 1). I have used the plastic cup exclusively since 1948.

It is interesting to note the difference in the percentage of pregnancies between the two methods—56 per cent and 83.3 per cent. It is also of importance to note that the average number of inseminations, as well as the average number of cycles required for pregnancy, was materially lowered when the plastic cup was used.

Another important feature is that no complications arose with the use of the plastic cup, whereas there were 5 complications (9.6 per cent) when the cannula was used. These complications included transient endometritis and 3 cases of acute pelvic inflammatory disease which required hospitalization, even though none of the semen was placed above the internal os.

Of the 134 pregnancies, 51 (60.7 per cent) were male infants and 33 (39.3 per cent) females. Four cases were lost because of incomplete follow-up, 24 patients miscarried and 22 remain undelivered. (table 2).

The average length of pregnancy from the day of conception to that of delivery was 267.2 days; that for males 264.7 and females 270.5.

Pregnancy followed a single insemination in 24 cases, and in 23 other cases, pregnancy followed with insemination in only one cycle, making a total of 47 patients that became pregnant in one menstrual cycle. The greatest number of inseminations performed on a patient who became pregnant was 34. Twenty-three patients received 10 or more inseminations before pregnancy occurred. There were no twins, moles or ectopic pregnancies. Two of the children were stillborn, though full term. One child was born with a hair-lip. Two patients required cesarean sections. Two patients now have had four pregnancies each, four have had three, 24 have had two by this method of insemination and the remaining 66 have had a single pregnancy.

The number of miscarriages in this series of artificial inseminations is about the same as reported for normal conceptions. Twenty-four of the 134 pregnancies miscarried (17.9 per cent). This percentage parallels the number of spontaneous abortions that might be expected in normal conceptions. Malpas[6] estimated an 18 per cent fetal loss, Whitehouse[7] 17.6 per cent, Mall[8] 20 per cent and Brunner

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[6] Malpas, P.: J. Obst. & Gynec. Brit. Emp., 45: 932, 1938.

[7] Whitehouse, B.: Proc. Roy. Soc. Med., 23: 248, 1929–30.

[8] Mall, F. P.: Am. J. Anat., 22: 49, 1917.

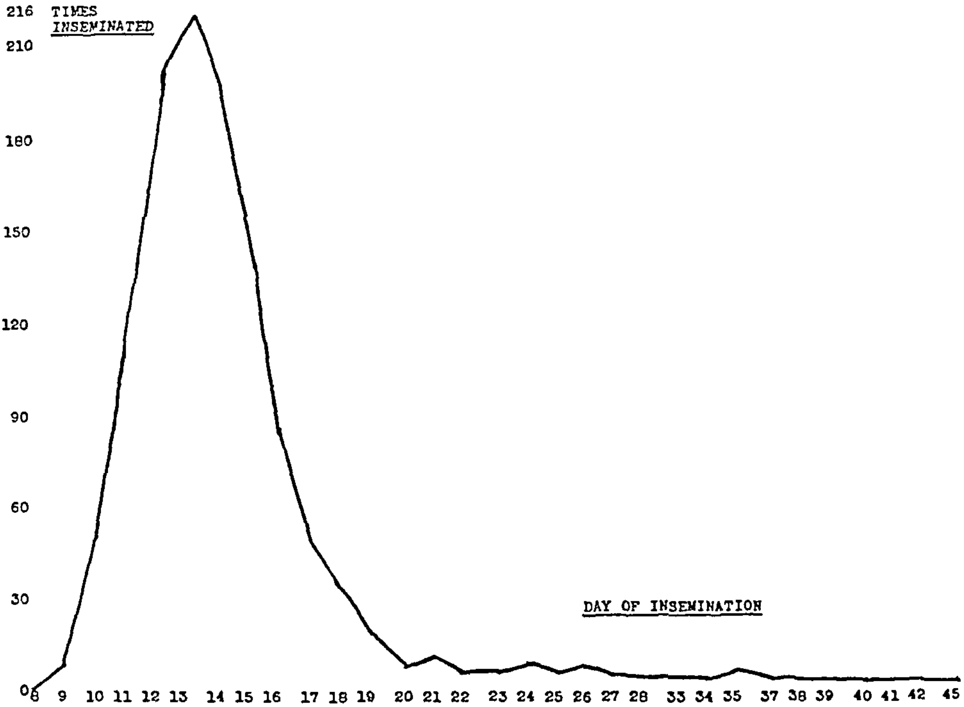

FIG. 1

and Newton[9] 15.8 per cent in their series of fertile matings, while Cary[10] reported 10.6 per cent of miscarriages in his series of 66 successful AID's.

Ovulation was considered to be between the low point in the mid-cycle and the beginning of the sustained rise which followed. Any insemination that occurred on either of these two days, or the day before the drop, was considered to have been inseminated at the time of ovulation. In the successful cases, even though insemination on ovulation day was performed 434 times, only 134 pregnancies resulted. Among those that did not become pregnant at all, 59 were inseminated 130 times on ovulation day with no success.

Seventy seven of the patients had regular cycles (varying four days or less) and of these, 64 became pregnant. Those patients whose cycles varied from 5 to 10 days, of which there were 72, had 50 pregnancies and 28 patients who had cycles varying more than 11 days showed 20 pregnancies.

A total of 63 donors were used during the series, some only once or twice, others more frequently. Only 27 of these donors were successful in impregnating these potentially fertile women, even though all of the donors were considered to be normal fertile males by our present standards. Five donors were responsible for 90 pregnacies, one donor siring 35, and another 22. There was no definite pattern of the results of the pregnancies. No one donor produced predominantly males or females and none was responsible for more than the average number of miscarriages. The other 22 donors produced the remaining 44 successes.

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[9] Brunner, E. K. and Newton, L.: Am. J. Obst. and Gynec. **38:** 82, 1939.

[10] Cary, W. H.: Results of artificial insemination with an extramarital specimen (semi-adoption). Am. J. Obst. & Gynec., **56:** 727–732, 1948.

TABLE 3

	DAYS PREGNANCY OCCURRED												
	10	11	12	13	14	15	16	17	18	19	21	23	24
Number of Pregnancies......	2	15	18	23	26	22	13	6	4	1	2	1	1

The day of insemination varied from day 9 to day 45 of the cycle. However, 81 per cent of the inseminations were performed between days 11 and 16 (fig. 1).

The fruitful inseminations occurred most frequently on days 13, 14 and 15, these days accounting for over half of the pregnancies (table 3). No pregnancies occurred when insemination took place before the tenth day or after the twenty-fourth day (fig. 2).

The number of patients who became pregnant within three months of insemination was 90, or 67.1 per cent of the total. Twenty-four additional women, making a total of 114, were pregnant within 6 months (86.2 per cent).

There was also a difference between the two methods in this respect. Without the cup, 16, or 57.1 per cent, were pregnant in 3 months as against 74, or 69.8 per cent, when the cup was used.

No court in the U.S., Canada or Great Britain has any statutory law aimed at artificial insemination.

The legitimacy of the child is presumed, as is all issue of a legal marriage. Only proof of the strongest character, by other persons, of the utter impossibility of the child's legitimacy can overcome this presumption.

Under California laws (and those of most of the Western states), any child born of a marriage when the husband and wife are living together and the husband is not impotent, is presumed to be legitimate. and if the foregoing two

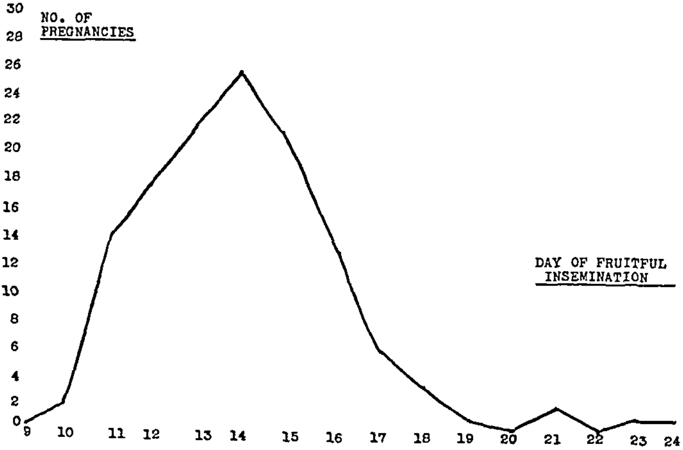

FIG. 2

conditions are met, this presumption is conclusive and indisputable (Civil Code, Sec. 194; Code of Civil Procedure, Sec. 1962(5)). However, the husband (or his descendants) has the right to offer proof that he was not cohabiting with his wife (as if he were "beyond the seas") during the time of conception or that he was impotent.

There is no agreed legal definition of this term, impotency, but several decisions involving the word seem to consider that impotency includes not only sterility but inability to copulate as well.

The suggestion has been made that adoption would solve the problem of the legitimacy of the child. Under California law (Sec. 224, Calif. Civil Code) a legitimate child cannot be adopted without the consent of both of its parents, if they are alive at the time of the adoption. Since all children born in wedlock are indisputably presumed to be legitimate, one would have the peculiar situation of the presumed parents attempting to adopt their own child. Therefore, the only natural assumption in that case would be that the husband was not the natural father of the child.

The method protecting the patients, the doctor and, more important, the potential child, is practiced in my office in the following manner:

Both husband and wife sign a consent giving permission to select a donor and to inseminate the wife, stating that they are living together as man and wife and that the husband is not impotent. Further, the couple understands that no guarantee is made that the patient will become pregnant, that she will carry to term or that there will be no malformation of the child.

This consent is signed by both husband and wife before a witness (my secretary) and is then placed in the patient's record. When the patient becomes pregnant, the consent is placed in an envelope in a safe deposit box, with the following written on the envelope, "To be destroyed without opening in the event of my death."

The donor has no opportunity to see the patient and the patient no opportunity of seeing the donor. Most specimens are brought to the office by me or by a messenger. Only the donor's number appears on the specimen bottle, and only the donor's number and date of artificial insemination is written into the history.

By using the foregoing methods, it has been possible to avoid emotional and legal complications to date. It is the most gratifying sensation in the world to see the parents bring the child to the office (a procedure that I demand) and see the expressions of pride and joy on their faces and hear from them the heartfelt gratitude to medical science that has made it possible for them to have such a wonderful child!

SUMMARY

The indications and prerequisites for insemination are reviewed.

The technique of using the plastic cup is briefly explained.

The timing of the insemination is based on the basal body temperature reading, the first insemination being performed 14–15 days before the shortest expected period.

One hundred seventy seven cases of artificial insemination where a donor's

semen was used is reported. One hundred thirty four pregnancies resulted from these inseminations (75.7 per cent).

The series is divided into two groups, those inseminated by instilling the semen onto the cervix and into the vagina, and those cases where a plastic cup was used to hold the semen against the cervix. With the old method, 56 per cent of the patients became pregnant and with the new method, 83.3 per cent of the patients were successfully inseminated.

The number of inseminations and the number of cycles necessary for pregnancy was materially reduced when the plastic cup was used.

The number of complications following inseminations was reduced to zero with the use of the cup.

Pregnancy ensued in 24 cases following a single insemination.

Thirty patients have had multiple pregnancies by artificial insemination.

The percentage of miscarriages (17.9 per cent) is about the same as expected in normal fertile matings.

Even though insemination was performed on ovulation day 564 times, only 134 pregnancies resulted (23.7 per cent).

Twenty seven of 63 donors accounted for all of the pregnancies, one donor impregnating 35 women.

Fruitful insemination occurred most frequently on days 13, 14 and 15; none before day 10 or after day 24.

Artificial insemination offers the possibility of bearing their own children to wives whose husbands are unable to produce offspring.

The use of the plastic cup is a valuable asset in artificial insemination.

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TRILENE* ANALGESIA IN UROLOGY

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The need for a safe, rapid, short analgesia devoid of the many unpleasant side effects commonly attributed to inhalation agents has long been recognized. Perhaps in no other branch of medicine except obstetrics is the need for such an agent more urgent than in Urology. The awareness of such a need prompted Dr. Young to write in his paper on self induction analgesia with nitrous oxide: "Cystoscopy, especially if prolonged for ureteral catheterization or endovesical operations, is occasionally a terrifying procedure."[1] The perception and response to painful stimuli vary with the individual and are influenced by many factors, such as age, sex, character, intelligence, apprehension or emotional state of the individual, and the nature of the disease. Emotionally stable individuals are inclined to be co-operative and show less outward reaction to pain, whereas those of excitable temperament often exhibit very violent reactions which are out of proportion to the painful stimuli. Apprehension may increase the response to pain while diversion tends to reduce or minimize this response.[2] It is this individual variation that permits us to perform most of our urologic examinations with only a local anesthetic. The use of local anesthetic agents, of which there are many, is helpful but often inadequate for extensive or difficult urologic procedures. In some instances urethral bleeding or individual sensitivity contraindicate their use. Routine use of general or spinal anesthesia for office procedures is impractical, requiring the use of cumbersome equipment and trained personnel. In addition, the hazards of general anesthesia must always be considered, and a period of prolonged recovery must be provided. These factors make it almost mandatory for such patients to be hospitalized, thus adding the burden of hospital costs and loss of income to the individual. Routine use of anodynes is often unsatisfactory and unwise, particularly in unaccompanied ambulatory patients. The constant search for an ideal anesthetic or analgesic agent led Hewer of England to investigate trichlorethylene.[3] The drug was previously used in the United States as an anesthetic agent by Stricker, Goldbladt, Warm, and Jackson in 1935.[4] The results of their study were inconclusive as is evident by a statement by the Council of Pharmacy and Chemistry of the American Medical Association in 1936 that "the case has not been completely made out" for the usefulness of the drug as a complete anesthetic agent.[5] Commercial grades of

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Read at annual meeting, Southeastern Section of American Urological Association, Havana, Cuba, March 26–29, 1953.

* Trilene (trichlorethylene) is a registered trade mark of Ayerst, McKenna and Harrison, Ltd., New York, N. Y.

[1] Young, H. H.: J. Urol., **41:** 95, 1939.

[2] Pickrell, K., Metzger, J., Wilde, N. J., Broadbent, T. R. and Edwards, B. F.: Plastic and Recon. Surg., **6:** 142, 1950.

[3] Hewer, C. L.: Brit. Med. J., **1:** 924, 1941.

[4] Stricker, C., Goldbladt, S., Warm, I. S. and Jackson, D. E.: Curr. Res. Anaesth., **14:** 68, 1935.

[5] Preliminary report of Council on Pharmacy and Chemistry, J. A. M. A., **107:** 1302, 1936.

trichlorethylene have been used in the dry cleaning industry and as a solvent for greases for many years These must not be used as an analgesic agent because of impurities which can give rise to toxic symptoms such as vomiting, vertigo, optic neuritis, and nerve palsy[6] Trilene is trichlorethylene purified and made suitable for anesthesia

CHEMISTRY

Trichlorethylene is a volatile liquid with an odor resembling chloroform Its chemical formula is $ChCl\ C\ Cl_2$ It has a specific gravity of 1 47 and a boiling range of 86 to 88 degrees C It is practically water insoluble and is not inflammable when mixed with any portion of air at ordinary temperatures and pressure

PHARMACOLOGY

The effects of Trilene on the central nervous system are characterized by a marked and rapid degree of analgesia which renders the drug useful for many minor procedures This is followed by loss of consciousness which is regained in a matter of seconds if low concentrations have been used This rapid return to consciousness and mental clarity permits the patient to be ambulatory and in command of all his faculties within a few minutes Its effect on blood pressure is usually negligible Cardiac arrhythmias are common when Trilene is used in high concentrations, but are uncommon when utilized in analgesic amounts Bradycardia, a precursor of cardiac arrhythmias, indicates increased vagal tone due to excessive amounts of Trilene[7] Tachypnea is also a sign of excessive vapor concentrations Bradycardia and tachypnea demand that the concentrations of vapor be reduced In contrast, simple hyperpnea reflects only the patient's response to intense stimulation Body metabolism is very slightly affected, if at all Gratifying to urologists is the absence of any demonstrable renal damage produced by this drug[7] Salivation or mucous secretions are not appreciably increased, making pre anesthetic drugs unnecessary Bleeding and clotting time are unaffected

CLINICAL USE

During the past two years we have used Trilene in over 100 selected cases, to determine the efficacy of this drug as an analgesic agent for various urologic procedures Most of these were treated as out patients in whom general anesthesia or heavy sedation was not practicable or advisable These particular patients were selected because a customarily painful or difficult procedure was anticipated In most cases, no special premedication was used We have used Trilene in performing the following procedures urethral dilatations, cystoscopy, cystoscopy and ureteral catheterization or dilatation, manipulation of ureteral calculi, ureteral meatotomy, urethral meatotomy, transurethral litholapaxy, biopsy of bladder tumor, incision and drainage of perinephric abscess, cystoscopic extraction of foreign body from bladder, removal and replacement of suprapubic mushroom catheters (See table 1)

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[6] Hewer, C L Proc Roy Soc Med , 36· 463, 1943

[7] Nowill, W K , Stephen, C R and Searles, P W Evaluation of trichlorethylene as an anesthetic and analgesic agent In publication

TABLE 1. *Urologic procedures under Trilene*

PROCEDURE	NO. CASES	AGE SPAN	RESULTS		
			Unsatisfactory*	Good	Excellent
Urethral dilatation	50	12–71	2	15	33
Diagnostic cystoscopy	20	13–74	2	4	14
Retrograde pyelography	14	10–71		5	9
Ureteral dilatation	4	34–59	1		3
Manipulation of ureteral calculi	3	21–45		1	2
Ureteral meatotomy	4	21–67		1	3
Urethral meatotomy	2	27, 44			2
Changing of suprapubic catheters	5	13–23			5
Transurethral litholapaxy	2	48, 49		1	1
Extraction of foreign body from bladder	3	50–71			3
Biopsy of bladder tumor	2	32, 54			2
Incision & drainage of perinephric abscess	1	28			1
Difficult catheterization	2	48, 68		1	1

* Unsatisfactory results were attributed to instrumentation before proper analgesia.

METHOD OF ADMINISTRATION

In all instances the drug was self-administrated with a Duke Trilene inhaler (fig. 1). The patient was instructed in the use of the inhaler, the purpose to be accomplished by its use and the correct positioning of the mask on the face. The dial indicator was set at the mark 3 so that the concentration of Trilene vapor

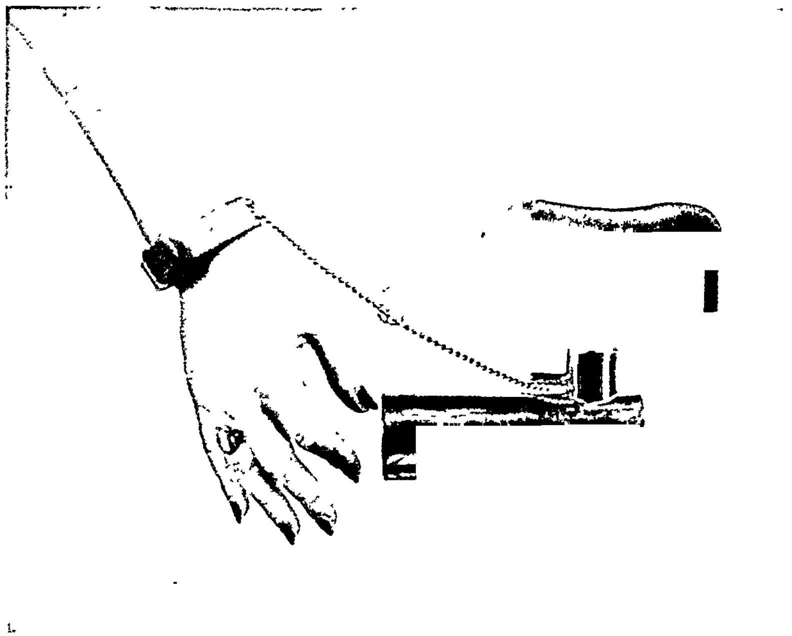

FIG. 1. Duke Trilene inhaler

received would be no greater than 0.6 volumes per cent.[8] He was allowed to take a few shallow inspirations in order to familiarize himself with the odor. He was assured he would not lose complete consciousness, but with the proper use of the inhaler, would be relieved of pain. We advised the patient to begin using the inhaler at the moment he was draped and during the interval in which we were preparing the cystoscope or other instruments for use. This allows approximately one to two minutes of inhalation prior to instrumentation. It is necessary to emphasize this point. The patient must have taken 20 to 30 inspirations before satisfactory analgesia is obtained. Painful stimulation before proper analgesia often causes the patient to become vociferous and unruly due to loss of inhibitions. Occasionally, with insufficient analgesia, a patient may exhibit a tonic contraction of extensor muscles as a result of painful stimulation. This reaction may be obviated by allowing adequate inhalation of Trilene before further instrumentation. By this routine of administration the patient is usually conscious and responsive and can co-operate throughout the procedure. If deep analgesia with loss of consciousness occurs, the hand and mask will drop away from the face allowing approximately two minutes more of painless instrumentation. By this method recovery of all cerebral functions occurs within a few minutes. These patients were checked for mental clarity by the use of simple mathematical problems and sense of direction. They were instructed to walk a straight line for sense of balance and in all instances were found to be in complete control of all faculties within a matter of five minutes or less.

OBSERVATIONS

From the physician's viewpoint, Trilene produces a rapid and marked analgesia and amnesia with minimal side effects. The simplicity and ease of administration eliminate the cost of cumbersome equipment or additional personnel. There is no excitement stage during induction. Premedication is unnecessary. The patient may be treated on an ambulatory basis and may leave the office within fifteen minutes. The occasional failures encountered have been due to improper or insufficient instructions in the use of the inhaler and hurried instrumentation before proper analgesia.

From the patient's viewpoint, Trilene has a pleasant odor. He possesses in his hands an agent to use at his discretion which will eliminate pain. It is devoid of many of the effects of other inhalation agents. It eliminates long recovery periods or possible hospitalization and generally simplifies the patient's visit to the urologist's office. The following cases and remarks are typical of the patients' responses to the use of Trilene.

M. S., aged 43, a white man, had multiple dense urethral strictures previously requiring dilatation under spinal or general anesthesia. He remarked that instruments had been passed by at least thirty different doctors and he regarded this instrumentation the easiest he had experienced. The patient has been returning at regular intervals to the clinic for urethral dilatations and each time requests the Trilene mask.

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[8] Hall, K. D., Garlington, L. N., Nowill, W. K. and Stephen, C. R.: Anesthesiology, **14:** 38, 1953.

B. S., aged 44, a white man, had two previous attempts at cystoscopy: the first under local anesthesia; the second with the use of 100 mg. Demerol and 0.1 g. sodium phenobarbital. Each time the attempted cystoscopy had to be discontinued because of pain. He has subsequently undergone cystoscopy twice, each time under Trilene and with complete freedom from pain. His reaction was that he could never have tolerated the procedure without the use of Trilene. Interestingly enough, this patient never lost consciousness, responded, and cooperated well throughout the procedures.

O. Y., aged 28, a Negress, was emaciated and debilitated from a long-standing perinephric abscess and considered by the anesthetist a poor anesthetic and operative risk. The perinephric abscess was incised and drained with breaking up of perirenal adhesions under the influence of Trilene. She complained somewhat during the procedure but had no recollection of pain after it was completed.

These are a very few typical examples of the patients' responses to the use of Trilene inhalation analgesia.

SUMMARY AND CONCLUSION

Trilene has been used in over one hundred urologic cases involving thirteen different urologic procedures with gratifying results. No alarming side effects have been observed. It possesses the following advantages:

1) Simplicity and ease of administration
2) Rapid induction and awakening
3) Marked analgesia and amnesia
4) Pleasant odor
5) Minimal side effects
6) Absence of excitement phase during induction
7) With momentary loss of consciousness, the mask falls from the face insuring maximum safety
8) Premedication, either local or systemic, is entirely unnecessary
9) Inexpensive
10) Marked assurance to the psyche

Prolonged or extensive surgical procedures do not come within the scope of Trilene analgesia and should be performed under the usual methods of surgical anesthesia.

It has been postulated that the ideal analgesic or anesthetic is one which is safe and complete and from which recovery is quick. It should be associated with minimal psychic trauma during and after induction followed by few if any side effects or complications. Trilene fulfills these qualifications as an analgesic agent.

Acknowledgment: My appreciation is expressed to W. K. Nowill and C. R. Stephen, Division of Anesthesia, Duke University for their friendly help and suggestions.

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COMMON HAZARDS OF X-RAY DIAGNOSIS IN UROLOGIC PRACTICE; THEIR RECOGNITION AND REDUCTION

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Since diagnostic x-rays are capable of causing serious injury,[1, 2] urologists should be aware of the risks involved in their use and should know how to protect patients, technicians, and themselves. Injury can be manifested by 1) anemia or leukopenia, 2) leukemia, 3) increased mutation rates, 4) fetal injury, 5) skin changes. Leukemia is reported to be nine times as frequent in radiologists as in nonradiologists.[3] The prospect of ever wider use of x-ray in Urology emphasizes the need for the urologist to utilize all safety precautions.

Total exposure during a day's work or a lifetime should be kept as low as possible, not merely below the current "maximum permissible exposure." This limit was lowered to one-half the previous value only four years ago, and it may be reduced still further in the future.

For details concerning radiation intensities about diagnostic x-ray equipment, the reader is referred to many excellent studies.[5, 6, 7, 8, 9]

Maximum permissible total body exposure is now 0.3 roentgen (r), or 300 milliroentgens (mr), per week. This is 50 mr per day for regular workers in radiation.[4] One milliroentgen is 1/1000th roentgen.

With a filter of 1.0 mm. aluminum in the primary beam, the patient's skin may receive from 0.5–1.5 r per exposure for a plain x-ray of the kidneys, ureters and bladder to 25 r for a lateral view of the pelvis. Without filter, the exposures are almost double. Scattered radiation from the patient is less intense but may be more penetrating than the primary beam. It must be remembered, however, that daily exposure to scattered radiation can result in much higher dosage to the doctor and technician than the patient receives from the primary x-ray beam at intervals separated by months or years. Measures which will reduce exposure of all concerned to reasonably low levels are simple, require little time or expense, and pay enormous benefits in safety and peace of mind.

Read at annual meeting, South Central Section of American Urological Association, Kansas City, Mo. September 21–23, 1953.

[1] Mossberg, H.: Platelet values in personnel engaged in roengten diagnostic work Acta Radiologica, 34: 186–192, 1950.

[2] Hultberg, Sven, Larsson, Lars-Eric, and Eklund, Lennart: Some cases of radiation injury in radiologic work. Acta Radiologica, 33: 376–387, 1950.

[3] March, H. C. Leukemia in radiologists in a twenty year period. A. J. M. Sc., 220: 282 286, 1950.

[4] National Bureau of Standards Handbook 41. Medical X-Ray Protection Up to Two Million Volts. National Committee on Radiation Protection, United States Dept. of Commerce, March 30, 1949.

[5] Sorrentino, Joseph and Yalow, Rosalyn. A nomogram for dose determinations in diagnostic roentgenology. Radiology, 55: 748–753, 1950.

[6] Keane, B. E. and Spiegler, G.: Stray radiation from diagnostic x-ray beams. Brit. J. Rad., 24: 198–203, Apr., 1951.

[7] Ritter, V. W., Warren, S. R., and Pendergrass, E. P.: Roentgen doses during diagnostic procedures. Radiology, 59: 238–251, 1952

[8] Martin, J. H.: Radiation doses received by the skin of a patient during routine diagnostic x-ray examinations Brit. J. Rad., 20: 279–283, 1947.

[9] Trout, E. D., Kelley, J. P., and Cathey, G. A.: The use of filters to [illegible] exposure to the patient in diagnostic roentgenology. A. J. Roent. & Rad. [illegible] 963, 1952.

The purpose of this paper is to point out the principal causes of overexposure to x-radiation in diagnostic Urology and to outline practical measures to reduce such hazards to a minimum. The principal dangers are from: 1) exposure to the primary x-ray beam, 2) exposure to scattered radiation from the patient, 3) unfiltered primary x-ray beam, 4) unlimited primary x-ray beam, 5) failure to employ radiation shields, 6) defective tubehead protection, 7) high MaS.-low KvP. techniques and 8) failure to measure actual radiation received.

Observation of the following principles will reduce the hazard to very low levels.

1. Never allow any part of the technician or urologist to be exposed to the primary x-ray beam unless absolutely necessary. When exposure is unavoidable, lead impregnated aprons and gloves should be worn.

2. Stay as far from the patient as possible, preferably outside the room, during actual x-ray exposures. Anyone inside the x-ray room should be behind a lead

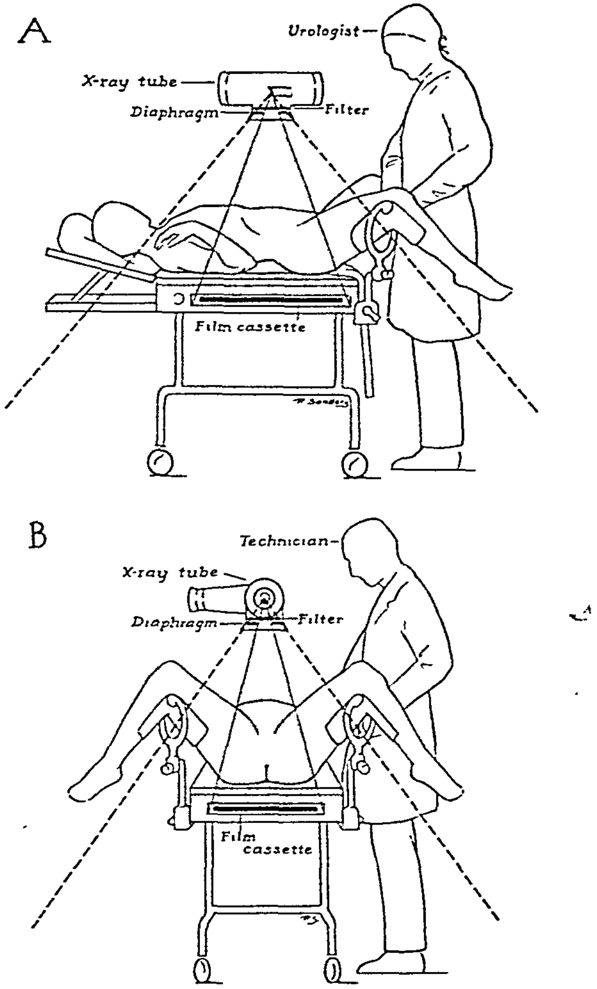

FIG. 1. *A*., diagram illustrating usual arrangement for retrograde pyelography, cystography, etc. Dotted line shows x-ray beam without diaphragm. Shaded area represents x-ray beam with diaphragm. *B*, illustrating relation of x-ray beam to technician standing beside urographic table. Dotted line shows x-ray beam without diaphragm. Shaded area represents x-ray beam with diaphragm.

protective screen. When contrast medium must be injected during the actual exposure, keep as far away as possible. If this occurs frequently, a protective apron should be worn or a screen employed.

3. Filter the primary x-ray beam with 2.0 mm. aluminum mounted permanently in the tubehead (fig. 1). This simple device reduces skin exposure to the patient about 75 per cent at medium kilovoltages, while requiring an increase of only 15–20 per cent in technique. Scattered intensities will be reduced also.

4. Limit the primary x-ray beam with a lead diaphragm (fig. 1). The beam should barely exceed the dimensions of a 14 by 17 inch film at the bucky tray level. Employ cones with smaller film sizes.

5. Stay behind a radiation shield if inside the x-ray room during an exposure. A smaller screen can be used very effectively by the urologist when he must remain nearer the patient. Never permit initiation of x-ray exposures with the bucky trip-string while standing by the x-ray table.

6. Completeness of tubehead protection against stray radiation is easily checked by surrounding the tubehead with cassettes, closing the useful aperture with lead, and making an exposure. Actual transmission in milliroentgens must be determined with a radiation survey meter.

7. High KvP.-low MaS. techniques reduce exposure to the patient compared to low KvP.-high MaS. techniques.

8. Use dental film badges routinely. This is a simple but effective objective check on the adequacy of all protective measures. It encourages safety consciousness and is definite evidence that exposure has or has not been low.

A film badge is made by fastening a lead number to the front of a dental film with adhesive tape. The badge is worn face outward on the clothing of the chest

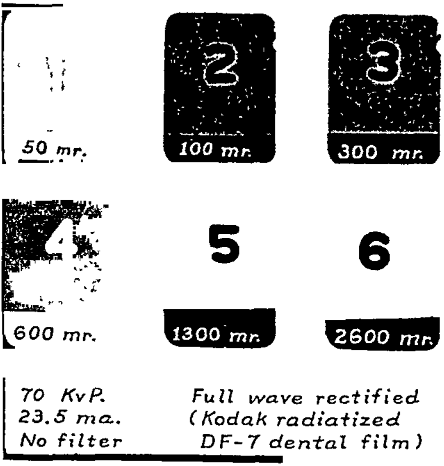

FIG. 2. Dental films exposed to various quantities of x-ray generated at factors shown

or abdomen, fastened with a safety pin. After one or two weeks, depending on volume of work done, the film is developed in regular x-ray solutions with an unexposed film as a control.

From 10 to 15 milliroentgens is required to blacken the film to a barely perceptible degree. Figure 2 illustrates dental films exposed to 50, 100, 300, 600, 1,300, and 2,600 milliroentgens. These are maximum permissible exposures for 1 day, 2 days, 1 week, 2 weeks, 1 month, and 2 months, respectively. The lower border of each film was shielded with lead and thus shows no radiation effect. The method is not quantitative except in a broad sense.[10] However, if the degree of blackening in one week or two weeks is distinctly less than that resulting from 50 mr, or one day's limit, it is obvious that exposure has been well below maximum levels. A definite medium or dark gray fog is clear warning of excessive exposure although not necessarily above maximum permissible. Defective shielding or careless violation of safety routines usually will account for the exposure.

Film badges are worn the first full work week of each month as a routine in the Department of Radiology, Parkland Hospital, Dallas, Texas by everyone working with or near x-ray machines. More than 100,000 diagnostic x-ray exposures are made per year, yet it is rare to find any perceptible exposure of a dental film.

If these safety practices are followed carefully, no harm to patients, physicians, or their assistants should occur.

SUMMARY

The possibility of injury from diagnostic x-rays in the practice of Urology is discussed.

The principal factors responsible for excessive radiation exposure are given.

Simple, effective means to reduce radiation hazards are outlined.

Routine use of film badges to indicate actual radiation exposure is recommended.

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[10] Tochilin, E., Davis, R. H. and Clifford, J. A.: Calibrated Roentgen-ray film badge dosimeter. Am. J. Roent. & Rad. Ther., 64: 475–488, 1950.

PROGRAM, ANNUAL MEETING OF NORTHEASTERN SECTION, AMERICAN UROLOGICAL ASSOCIATION, QUEBEC CITY, CANADA, SEPTEMBER 20-22, 1954

SEPTEMBER 20

A Case of Tetany in Uremia, Responding to Therapy, Albert G. Rowe, Hornell, N. Y.
Discussion. To be opened by William E. Ortved, Toronto, Canada

Porphyria: A Medical Condition Presenting a Surgical Problem, N. E. Berry, Kingston, Ontario, Canada
Discussion.

Experience with Complications Following Urologic Surgery, W. J. McMartin, President A.U.A. (by invitation), Omaha, Nebr.
Discussion.

Surgical Treatment of Horseshoe Kidneys: Comparison of Results after Various Types of Operations, O. S. Culp (by invitation), Mayo Clinic, Rochester, Minn.
Discussion.

Prostatectomy, Then and Now, F. J. Parmenter, Buffalo, N. Y.
Discussion. To be opened by George E. Slotkin, Buffalo, N. Y.

SEPTEMBER 21

Surgical Excision of Tumors Involving the Bladder Neck and Prostate, Elmer Hess, Russell B. Roth and Anthony F. Kaminsky, Erie, Pa.
Discussion. To be opened by Elmer Hess, Erie, Pa.

Movie: The Use of X-ray Motion Picture to Study Bladder and Urethral Function in Man and Dog, John A. Benjamin, Rochester, N. Y.
Discussion. John A. Benjamin, Rochester, N. Y.

Reflections on Some Problems Relating to Uretero Sigmoid Anastomosis, Reed M. Nesbit (by invitation), Ann Arbor, Mich.
Discussion.

Experiences in the Treatment of Carcinoma of the Bladder with Radioactive Isotope of Gold, J. L. Hamilton, Pittsburgh, Pa.
Discussion. Conrad A. F. Kuehn, Pittsburgh, Pa.

Hydatid Cyst of Kidney, R. Grant Reid, Montreal, Canada.
Discussion. To be opened by H. L. Schlesinger, Plattsburg, N. Y.

Presidential Address, Dr. Albert M. Crance, Geneva, N. Y.

SEPTEMBER 22

Clinical Statistical Survey of Renal Tumors Encountered in Our Practice, Patrick S. Mullins, Utica, N. Y.
Discussion. To be opened by David W. Kline, Greenville, Pa.

Tumors of the Urinary Bladder: A Clinico-Pathological Analysis of over 2000 Specimens and Biopsies, M. M. Melicow (by invitation), New York, N. Y.
Discussion.

Management of Urethral Carcinoma in the Female, William J. Staubitz, Lawrence M. Carden, Oscar J. Oberkircher and Melbourne H. Lent, Buffalo, N. Y.
Discussion. To be opened by M. M. Melicow, New York, N. Y.

Lesions of the Kidney in Acute Renal Failure, Douglas Waugh (by invitation), Montreal, Canada
Discussion.

Wilms's Tumor, A. B. Hawthorne, Montreal, Canada.
Discussion. To be opened by Douglas Waugh, Montreal, Canada.

Vesical Neck Obstruction in the Female, Ernest F. Hock, Binghamton, N. Y.

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South Central Section—Colorado Springs, Colo., October 18–20, 1954
Western Section—Hotel del Coronado, Coronado, Calif., January 24–27, 1955
Southeastern Section—Hotel Jung, New Orleans, La., March 21–23, 1955
Mid-Atlantic Section—Haddon Hall, Atlantic City, April 13–16, 1955

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ADRENAL INSUFFICIENCY AS RELATED TO SURGICAL SHOCK

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The hazards of surgery are well appreciated in relation to patients having known adrenal insufficiency, such as Addison's disease.[1] Certain effective precautions are taken to prepare for and combat the shock and electrolytic imbalance that are to be anticipated. Acute adrenal cortical insufficiency, moreover, may also occur as a serious postoperative complication in patients not previously known to have adrenal disease. Such a distressed patient may fail to survive if the hypo-adrenalism remains unconsidered and unrecognized, for the essential therapy will not be supplied. For reasons to be given, we believe the urologist should be particularly alert to the possibility of acute adrenal insufficiency developing incident to the stress of an operation.

The clues for the diagnosis and the rationale of treatment of hypo-adrenalism are based upon the principles of adrenal physiology. It would therefore be appropriate to review the hypothalamus pituitary adrenal cortical axis for this neuro-endocrine complex is concerned with stress and the physiologic reactions thereto.

PHYSIOLOGY

The hypothalamus receives and responds to the stimuli of stress thereby releasing the corticotrophin hormone (ACTH). See figure 1. ACTH, in turn, is responsible for the elaboration of three groups of steroid hormones in the cortex of the adrenal glands. The stress phenomenon concerns principally the mineral corticoid group, of which desoxycorticosterone is an important member, for salt and water metabolism is profoundly affected by this group. A second group of adrenal hormones, designated as the glucocorticoids, are concerned primarily with the metabolism of fat and the conversion of protein to carbohydrates. In their absence the organism must rely completely on carbohydrate stores with a consequent depletion of the glycogen content of the liver. A third group of adrenal hormones is known as the androgenic steroids, but their functions are not particularly germane to the topic under discussion.

The effects of adrenalectomy in the experimental animal are well known. Comparable physiologic alterations develop in the postoperative patient if there is an inadequate release of corticoids in response to the stress of surgery. The primary changes noted in acute adrenal insufficiency precipitated by surgical stress are: a) an immediate, rapid, loss of sodium and chloride from the blood serum with concomitant increase in their concentration in the urine; and b) a marked decrease in the vascular space with consequent hypotension and a decreasing urinary output terminating in anuria.

Accepted for publication February 18, 1954.

[1] Thorn, G. W.: Diagnosis and Treatment of Adrenal Insufficiency. Springfield, Ill.: Charles C. Thomas, Publisher.

HYPOTHALMUS-PITUITARY-ADRENAL CORTICAL AXIS

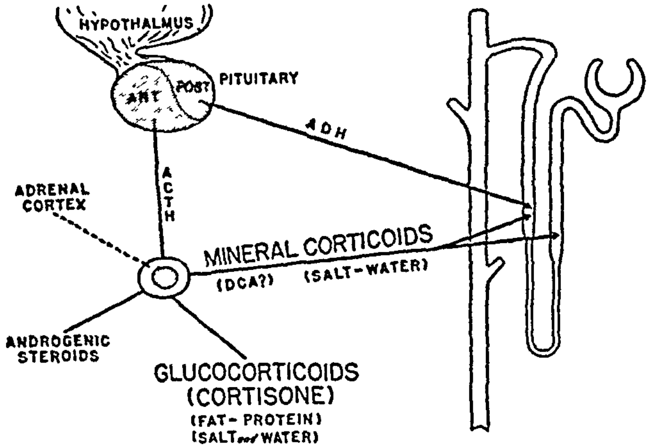

FIG. 1

The equilibrium between serum sodium, intracellular sodium, and the urinary excretion of sodium is partly dependent upon the mineral corticoids and the antidiuretic hormone of the pituitary. The antidiuretic hormone remains unopposed if the mineral corticoids are not provided thereby producing an oliguria. Water shifts from the vascular space into the interstitial and cellular compartments of the body.[2-4] See figure 2. Hypotension ensues and contributes to the reduced production of urine by diminished renal blood flow. These violent physiologic disturbances are augmented by loss of serum sodium due to increased excretion into the urine. The serum potassium and serum urea nitrogen increase, presumably because of reduced renal clearance.

The degree of shock is dependent, in the norm, upon the magnitude of the stress. The compensatory output of corticoids during the recovery phase is regulated by the requirements necessary to restore the body equilibrium. If these hormones are not available in sufficient amounts, such as in adrenal insufficiency, DCA may be administered as a substitute. Salt is then retained, water shifts back from the cells to the vascular space, the blood volume is restored, the blood pressure rises and diuresis is precipitated, for the adrenal hormones now oppose the pituitary antidiuretic hormone. With resumption of renal function there is increased clearance of potassium and urea, allowing a return to normal blood levels. The glucocorticoids (cortisone) have a relative minor effect upon the regulation of salt and water as compared to the mineral corticoids (DCA). Nevertheless, if cortisone is given in excessive amounts over a period of time, salt and water will be retained in the body.

It is quite apparent that a valuable purpose would be served if some simple test could be applied to appraise the reliability of the adrenals to produce sufficient corticoids to defend the body adequately against the stress of a contemplated surgical procedure. It must be borne in mind that failure to respond

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[2] Loeb, R. F.: Bull. N. Y. Academy of Med., 18: 263-270, 1942.
[3] Harrop, G. A.: Bull. Johns Hop. Hosp. 59: 11-23, 1936.
[4] Smith, Homer: The Kidney. New York: Oxford University Press, 1951.

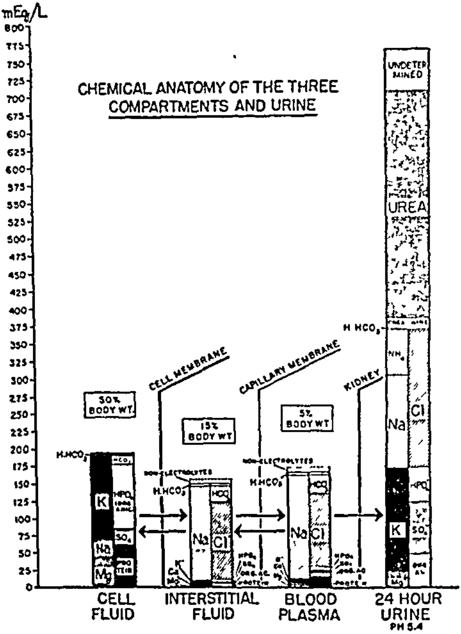

FIG. 2

may occur at any of the three levels of the hypothalmus-pituitary-adrenal axis. There are no chemical tests to evaluate the hypothalmic area. At present there is no specific differentiating test for pituitary insufficiency. Formerly, a test for pituitary function was used based upon the premise that epinephrine acted upon the hypothalmus thereby stimulating the pituitary to release corticotrophin. The adrenals, in turn, were then activated causing a fall in the circulating eosinophiles from the previously determined control levels. Pituitary insufficiency was inferred if this drop in eosinophiles failed to develop but was obtained by exogenously administered ACTH. Recent studies in bilaterally adrenalectomized man have shown, however, that epinephrine is capable of producing eosinopenia in the absence of adrenal cortical tissue, thus invalidating the test.

A number of tests have been advocated to determine the capacity of the adrenal cortex to respond to corticotrophin. These have included determination of the 17-ketosteroids and the neutral reducing lipids (11-oxysteroids). The measurement of the 17-ketosteroids urinary output includes the androgenic precursors from both the adrenals and testes and therefore is not an indicator for the adrenal alone. On the other hand, the 11-oxysteroids reflect the production of the glucocorticoids which arise only from the adrenals and probably indicate the total corticoid potentials of the adrenals. Adrenal cortical insufficiency may be detected by a clinical test utilizing these principles. Following the intravenous administration of twenty U.S.P. units of ACTH there is an increase in the 17-ketosteroid urinary excretion of ten to fifteen milligrams (10–15 mg.) above the control level. This is accompanied by a fall of at least eighty-five per cent of the circulating eosinophiles from control levels. Failure to secure these responses indicates primary adrenal cortical insufficiency.[5, 6]

Two other clinical tests of proven value have been employed to diagnose hypo-adrenalism. The Robinson-Kepler-Power water test employs the principle that an individual with hypo-adrenalism excretes less urine following the ingestion of a large quantity of water than does a normal. An intake of 1500 cc water over a 40 minute period will normally result in the excretion of 1200 cc urine during the ensuing 5 hours. A person with Addison's disease is unable to develop diuresis because of unopposed action to the antidiuretic hormone and accordingly will excrete less than 800 cc within that time. The "Salt Deprivation Test" operates upon the fact that an individual with Addison's disease continues to lose salt via the kidney even though he is deprived of dietary sodium. The normal person promptly reduces the amount of excreted salt to conserve his endogenous supply. Within two to six days a crisis will develop in hypo-adrenalism due to salt deficiency, whereas the absence of such a response in a suspected patient makes the diagnosis of Addison's disease untenable.[7]

The foregoing tests are designed to diagnose adrenal insufficiency before an actual crisis develops. Often, however, the surgeon is confronted with unexplained postoperative shock which does not respond to the usual methods of treatment and one may well suspect that the stress of the operation has precipitated adrenal cortical failure. The diagnosis may be supported by four findings: 1) marked hypotension, 2) low blood serum sodium, 3) low blood serum chloride and 4) low carbon dioxide combining power. The serum sodium and chloride determinations are valuable indicators of adrenal function but the diagnosis of hypo-adrenalism cannot be rejected if normal levels are encountered. The hemoconcentration accompanying the adrenal crisis may mask the actual loss of total serum electrolytes by virtue to higher concentration per unit of blood serum. Furthermore normal levels of these electrolytes may prevail in the presence of adrenal insufficiency unaggravated by the stress of surgery, so that serum sodium and chloride determinations prior to surgery are not effective "screening" procedures.

How then is it possible to prepare for a crisis or diagnose adrenal insufficiency if suspected as a postoperative catastrophe? One or more of the foregoing clinical tests may be employed prior to surgery and appropriate prophylactic treatment begun, if indicated. If unexplained shock develops following surgery which is refractory to usual supportive therapy, substitution adrenal therapy may be a life saving measure. Low blood serum sodium chloride and base are valuable aids to support such an assumption.

[5] Thorn, G. W.: J. Clin. Endocrinol., **13**: 614–616, 1953.
[6] Thorn, G. W.: J. Clin. Endocrinol., **13**: 604–613, 1953.
[7] Soffer, L. J.: Bull. N. Y. Acad. Med., **29**: 101–103, 1953.

It is of advantage to know what type of patient may develop a crisis after an operation. Such might be encountered in one of the following groups.

1) Patients subjected to an extensive surgical procedure.
2) Senile patients with chronic debilitating disease.
3) Psychotic patients.
4) Patients who have urologic disorders.
5) Patients who have been treated with cortisone, hydrocortisone, and/or corticotrophin.

1) *Extensive surgical procedures.* Zimmerman made observations on two groups of patients and recorded results which he attributed to be due to differences in cortical responses to stress.[8] Operations which ordinarily do not produce shock were compared with extensive procedures. Patients who had drastic surgery demonstrated a prolonged fall in serum sodium and chlorides, whereas the changes were less marked when the operation was not severe. He concluded that unusually severe operative stress may exhaust the adrenals, producing a period of relative adrenal insufficiency.

2) *Senile patients with chronic debilitating disease.* With advancing age the 17-ketosteroid output decreases. Bonner has shown that a decreased uric acid response to corticotrophin is to be expected in aged and debilitated patients.[9] Selye has referred to patients in the advanced age group as having poor adaptation to chronic stress. The conclusion drawn from these studies is that this group of patients has subclinical adrenal insufficiency.[10-12]

3) *Psychotic patients.* The psychotic patient has been extensively studied in terms of adrenal activity. Pincus and Hoaglund reported 72 per cent hyporesponsitivity in schizophrenia, using the indices previously mentioned.[13-17] The deficiency was thought to be localized to the adrenal cortex and was not of pituitary origin. Grunebaum confirmed their work utilizing studies on the salt content of sweat.[18] The high perspiratory sodium indicates a deficiency of the adrenals in the regulation of salt in psychotic patients.

4) *Patients who have urological disorders.* Special situations confront the urologist in surgical care in addition to the common problem of age and debilitation. Patients who have had previous renal surgery may have suffered unrecognized but irreparable damage to the corresponding adrenal incident to manipulation of the kidney. The accidental removal of an adrenal is possible during difficult nephrectomy. If surgery becomes necessary on the remaining or unoperated kidney the solitary adrenal might also be traumatized so that its function is impaired during the immediate postoperative period. Furthermore,

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[8] Zimmerman, B.: Surgical Forum. Philadelphia: W. S. Saunders Co., 1951.

[9] Bonner, C. D.: Geriatrics, 5: 203-207, 1950.

[10] Kowalewski, K.: J. Gerontology, 5: 222-225, 1950.

[11] Goldsieher, J. W.: Gerontology, 7: 47-53, 1952.

[12] Timiras, P.: Geriatrics, 4: 225-229, 1949.

[13] Pincus, G.: Am. J. Psych., 106: 651-659, 1950.

[14] [illegible], 1946.

[illegible] 1949.

[illegible] 1946.

[illegible] -88, 1949.

[illegible] eurol. & Psych., 63: 444-452, 1950.

unilateral congenital absence of the adrenal presents an uncommon but definite hazard during kidney operations. Metastatic carcinoma of the prostate has been known to replace both adrenals and extensive involvement of the adrenals by tuberculosis is always a possibility when the tuberculosis of the genito-urinary organs requires surgery. Atrophy of the contralateral adrenal in instances of adrenal tumor is so well known that further comment is unnecessary. Two common practices deserve attention in relation to urologic patients. The custom of forcing fluids after operation may constitute a most effective Robinson-Kepler-Power water test in the aged patient with hyporesponsive adrenals. Significant water retention due to the unopposed action of the antidiuretic hormone may result. Secondly, the urologist often withholds parenteral saline during the first few postoperative days, for good reason, with patients having cardiac disease. Salt deprivation coupled with adrenal exhaustion may produce a crisis as described in the salt deprivation test for Addison's disease.

5) *Patients who have been treated with cortisone, hydrocortisone and/or corticotrophin.* There is considerable evidence to support the view that the therapeutic administration of adrenal cortical hormones may suppress adrenal function and induce atrophy. Corticotrophin and cortisone also may produce histologic alterations in the pituitary gland impairing the production of endogenous corticotrophin. These atrophic changes may lead to acute adrenal cortical insufficiency in the face of sufficient stress, such as an operation. Salassa and associates conclude that "any patient who has received sufficient cortisone within three to six months should receive prophylactic therapy," before an operation.[19] Adrenal suppression may occur with a minimal dosage after only 5 days of treatment and render the individual susceptible to a crisis long after the treatment has been discontinued. Consequently, all patients who have had prior treatment with these hormones should, at least, be observed with greatest care and treated promptly if signs of hypo-adrenalism develop following an operation.

ILLUSTRATIVE CASES

The following case studies are presented as examples of proven adrenal insufficiency or, as illustrations of severe shock following stress apparently relieved by substitution therapy.

Case 1. Admission No. 10140 (1947) Bellevue Hospital. A 72 year old man was admitted to the Department of Urology, Bellevue Hospital in 1947 with a diagnosis of recurrent bladder tumor. He had had numerous admissions for transurethral fulguration of this lesion, but had consistently refused more extensive surgery. His blood pressure on admission was 150/90. The physical examination was essentially negative. Cystoscopy on this admission revealed a sessile neoplastic lesion. A cystotomy was done and the tumor was fulgurated by electrocautery. During the operation unexplained shock developed and the patient's blood pressure fell to 80/50. He failed to respond to the usual therapy for surgical shock and expired within thirty hours after operation without having regained consciousness. His blood pressure remained at shock levels until his death.

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[19] Salassa, R. M.: J.A.M.A., 152: 1509–1515, 1953.

Autopsy revealed complete replacement of both adrenals by metastatic tumor. The para-aortic glands were similarly involved.

Comment: This proven case of adrenal insufficiency was completely unsuspected prior to operation. Adequate treatment to reverse the insufficiency was unavailable at that time.

Case 2. Admission No. 82113 (1951) Bellevue Hospital. W. L., a 66 year old white man, was admitted to the Neuropsychiatric Division of Bellevue Hospital in 1951, with a long history of prostatism. System review and physical examination revealed an apparently healthy adult male, appearing younger than his stated age. His blood pressure was 170/80 and his prostate was two times enlarged and of benign consistency. An excretory urogram revealed a large vesical calculus, a hydronephrotic right kidney, and a nonfunctioning left kidney.

A suprapubic cystolithotomy was done with almost no loss of blood. The patient experienced no difficulty until 48 hours after operation, when unaccounted for profound shock suddenly developed. His blood pressure was recorded as 70/0. Routine therapy for shock was instituted, and during the next 24 hours he received oxygen, 750 cc plasma and 1,000 cc of whole blood in addition to parenteral fluids. His general condition remained unchanged and he became anuric. Blood serum revealed a chloride of 80 mEq/L (normal 104) and serum sodium of 114 mEq/L (normal 140–145).

Adrenal hormonal therapy was given together with parenteral sodium chloride therapy. His blood pressure quickly rose to preoperative levels, diuresis promptly began, and he recovered from the state of shock. His electrolytes reverted to normal within the next five days with the exception of an elevated blood serum nonprotein nitrogen which was attributed to his pre-existing renal disease.

A transurethral resection of the prostate was recommended but the patient refused consent to this procedure. When examined at subsequent visits to the hospital following his discharge, he was without evidence of clinical hypoadrenalism. The 24 hour 17-ketosteroid output one month after recovery was 1.5 mg.

Case 3. Admission No. 2752 (1952) Bellevue Hospital. M. B., an 84 year old white man, was admitted to the Neuropsychiatric Division of Bellevue Hospital. He had been transferred from another hospital where he had become unmanageable. A history suggestive of prostatic obstruction of many years' duration was obtained from relatives. He was found to have an enlarged heart, hepatomegaly, and benign prostatic hypertrophy producing residual urine to the amount of 250 cc. His blood pressure was 230/100. Restraints were constantly required to prevent him from removing his catheter. Despite sedation, he was under constant emotional and physical stress protesting and struggling to free himself from his restraints. At the end of 24 hours the patient's blood pressure rapidly fell to imperceptible levels. His skin was cold and clammy and the 24 hour output of urine decreased to 200 cc despite an adequate intake of fluids.

Blood samples were secured at this time and analyses revealed the following: Sodium, 116 mEq/L; chloride, 70 mEq/L; carbon dioxide combining power, 30 volumes per cent.

Adrenal cortical hormones and parenteral sodium chloride were given. Within 48 hours, the patient's blood pressure was restored to the former hypertensive levels and his serum electrolytes returned to normal. A twenty-four hour 17-ketosteroid output was 1.3 mg.

A suprapubic cystotomy was done on the fourteenth day after admission. The patient experienced no difficulty for the first 48 hours but thereupon sudden profound shock developed. Adrenal substitution therapy and parenteral saline were again resumed. Serum electrolytes before therapy revealed the following: Sodium, 106 mEq/L; chlorides, 78 mEq/L; and carbon dioxide combining power 42 volumes per cent. The signs of shock were promptly controlled, his blood pressure was restored, and within 48 hours his serum electrolytes were normal. Three weeks later, prophylactic adrenal substitution therapy was given and a suprapubic prostatectomy was performed without signs of shock, or with any clinical or laboratory evidence of adrenal insufficiency. However, on the fourth postoperative day, broncho-pneumonia developed which failed to respond to therapy. The patient died on the eighth postoperative day. No autopsy was obtained.

Case 4. Admission No. 14746 (1952) Bellevue Hospital. L. G., an 84 year old man, psychotic, and blind secondary to glaucoma, had known arteriosclerotic heart disease with previous episodes of failure, and suffered from Parkinson's disease. There was a 6 year history of prostatism and he was admitted to Bellevue Hospital in acute urinary retention. His prostate was enlarged and nodular. The blood serum phosphatases were normal and there was no roentgen evidence of skeletal metastases.

After 8 days of catheter drainage, a transurethral prostatectomy was done. During the operation the blood pressure suddenly fell to imperceptible levels and was restored and maintained at 70/0 only by continuous intravenous neosynephrine. Adrenal cortical hormones and parenteral saline were given and within one hour the neosynephrine was discontinued. Samples of blood taken at this time revealed sodium, 113 mEq/L; potassium, 3.8 mEq/L; chloride, 82 mEq/L. His blood pressure rose promptly to 130/70 as compared to 170/84 prior to operation. Blood serum electrolytes 24 hours later were sodium, 130 mEq/L; potassium, 2.7 mEq/L; chloride, 138 mEq/L.

During the following week signs of cardiac failure gradually developed as evidenced by pulmonary and peripheral edema. Despite fluid restriction, elimination of sodium and chloride, the use of diuretics and potassium, he died 8 days following surgery. His death was primarily attributed to heart failure.

Comments. Cases 2 and 3 were elderly psychotic, chronically ill men with multiple system diseases. Each experienced severe shock after a surgical procedure although such could not be explained by blood loss or untoward events in the conduct of the surgery. The conventional methods for combating shock were not rewarding but treatment designed to provide corticoids and correct electrolyte imbalance appeared effective in overcoming the immediate crisis.

Case 4 illustrates the multiplicity of problems inherent in attempting to maintain electrolyte and water balance in the presence of congestive heart failure complicated by probable adrenal insufficiency. Sodium and chloride blood serum levels were excessive on the second postoperative day. As a result we have since discontinued the use of 5 per cent sodium chloride infusions and now employ only isotonic sodium chloride. There have been no other instances of higher than normal levels of sodium and chlorides since salt has been used more sparingly.

Case 5. Admission No. 8978 (1953) Bellevue Hospital. H. S., a 68 year old man, was admitted to the Fourth Surgical Division (Urology) of Bellevue Hospital with a history of gross hematuria on three occasions during the year prior to admission. Two years previously, stones had been removed from each kidney.

The patient's blood pressure on admission was 170/100. The physical examination was essentially negative except for bilateral loin scars. Urologic investigation revealed numerous calculi in a hydronephrotic left kidney. There were several small right renal calculi. Nonprotein nitrogen was 50 mg. per cent.

A left nephrolithotomy was done with moderately severe blood loss which was replaced immediately. Following the operation, the patient's blood pressure remained quite labile despite further blood transfusions. Twenty-four hours after operation the blood pressure dropped to 70/30 and the patient lapsed into severe shock. Adrenal cortical hormones and parenteral sodium chloride were given, after appropriate electrolyte studies had been done. Without further transfusions the patient's blood pressure rose to 150/70 within two hours, and remained stable at that level. His urinary output, which had been 300 cc in the previous 24 hours, increased to 1600 cc in the second 24 hour period. The patient was maintained on adrenal cortical hormones for one week and made an uneventful recovery. Serum electrolyte studies prior to the initiation of hormonal therapy were not remarkable, as revealed by the following: Sodium, 123 mEq/L; potassium, 4.5 mEq/L; chloride, 92 mEq/L.

Comment. The prompt response to this regimen strongly suggests that adrenal cortical insufficiency accounted for shock, hypotension, oliguria, and collapse.

Case 6. Admission No. K57190 (1952) University Hospital. A 52 year old woman was admitted to University Hospital with a diagnosis of recurrent staghorn calculus in a solitary kidney. The contralateral kidney had been removed some years previously for calculous pyonephrosis. The right kidney had been operated upon by one of us (R. S. H.) 18 months previously, at which time a nephrolithotomy and a ureterotomy for stricture were performed.

The kidney was again freed, the pedicle clamped with rubber shod clamps, and a kidney split performed to remove a large staghorn calculus. At no time during the procedure was there excessive bleeding and the apparent blood loss was replaced during operation. One hour after completion of the surgery the patient's blood pressure fell to 50/20 accompanied by profound shock. There was no evidence of unusual postoperative bleeding. Adrenal cortical hormones and parenteral saline with neosynephrine were given by the intravenous route. The clinical response was immediately satisfactory and within 12 hours the neosynephrine was discontinued. On the third postoperative day an electrolyte survey revealed normal serum sodium chloride, carbon dioxide combining power, and nonprotein nitrogen. An uneventful convalesence followed.

Case 7. Admission No. K51292 (1952) Bellevue Hospital. J. S., a 64 year old man, who had had a prostatectomy one month previously in another hospital was admitted to the Fourth Surgical Division (Urology), Bellevue Hospital. On his first postoperative visit to his urologist, urethral dilatation was done and he fainted. Following his recovery he returned home and once again collapsed. When admitted to Bellevue Hospital, 2 hours later, he was in profound shock. His blood pressure was unobtainable and his pulse weak. There was no evidence of a rupture of the bladder or of the urethra. The patient remained stuporous, hypotensive, and oliguric for the next 24 hours despite vigorous antishock treatment. He was then given adrenal cortical hormones and parenteral saline. Within four hours his blood pressure had risen to 110/60 and his skin was dry and warm. A diuresis followed and he made an uneventful recovery. Subsequent investigations, including electrocardiography, failed to reveal any specific demonstrable cause for his cardiovascular collapse.

Case 8. Admission No. K55951 (1952) University Hospital. Miss M. M., a 23 year old girl and a known schizophrenic, was admitted to University Hospital because of persistent right renal pain and pyuria. Retrograde studies revealed caliectasis in the upper pole of the right kidney. Urinary sediment was searched for tubercle bacilli but none were found. An abscess of the upper pole of the right kidney was discovered and drained when the kidney was exposed. A febrile postoperative course led to the conclusion that a perinephric abscess had developed. Three weeks after the first operation the wound was opened and a large perinephric abscess was discovered. A nephrectomy was done and drains were left in the fossa. Within 6 hours her blood pressure fell to 40/0 and she exhibited all signs of severe shock. It was assumed that the difficulties could be attributed to postoperative hemorrhage at the site of the renal pedicle. Multiple transfusions were given without improvement and within 6 hours she was returned to the operating room. The wound was opened but, as no hemorrhage had occurred, it was closed. Adrenal cortical hormones and parenteral saline were then given, and additional transfusions were withheld. The patient's blood pressure rose to preoperative levels within 2 hours, and at no subsequent time was there cause for concern. Decreasing amounts of cortisone were given for the next 2 weeks and she was discharged without complaints.

Comments: Cases 6, 7 and 8 suffered severe shock following stress. The blood electrolyte studies were not secured to support the assumption that hypoadrenalism was the major factor causing distress, for the sudden onset and extreme severity of symptoms demanded prompt emergency treatment. The response to corticoids, when other methods failed, persuade us to conclude that specific effects had taken place which, indeed, were life saving measures.

PLANS OF TREATMENT

Schedule I. Prophylactic Treatment

Should a diagnosis of adrenal insufficiency be established prior to operation, some form of prophylaxis is indicated. The regimen used on the Fourth Division

Urology, Bellevue Hospital is similar to that employed prior to adrenalectomy for prostatic carcinoma.

Day before surgery.

5 mg. desoxycorticosterone acetate in oil intramuscularly.

Cortisone 50 mg. intramuscularly every 6 hours to a total 200 mg. Blood serum sodium and chloride.

Day of surgery.

5 mg. desoxycorticosterone acetate.

50 mg. cortisone every 4 hours.

Pulse, temperature and blood pressure recorded every 2 hours.

Morphine and related substances used sparingly.

First postoperative day.

3 mg. desoxycorticosterone.

50 mg. cortisone every 6 hours.

Blood serum sodium and chloride.

Second postoperative day.

1 mg. desoxycorticosterone.

50 mg. cortisone every 8 hours and thereafter, gradually reduced as indicated on subsequent days. The patient should receive 1000 cc of 5 per cent glucose in isotonic saline intravenously on the day of operation, plus whatever additional parenteral fluids are considered advisable as determined by the patient's response to operation and his preoperative dietary regimen.

Schedule II. Active Therapy

Active therapy for acute adrenal insufficiency developing in a patient not previously suspected of adrenal cortical insufficiency.

Hormones.

10 mg. desoxycorticosterone acetate in oil intramuscularly every hour for 3 doses.

50 mg. cortisone intramuscularly every 2 hours until the systolic pressure is maintained above 100 mm. of mercury. The subsequent hormonal requirements are judged according to the patient's response. (See Schedule I).

Fluid and electrolytes.

1) One thousand cubic centimeters of 5 per cent glucose in isotonic saline is started at once at the rate of 60–80 drops per minute. A second infusion of 1000 cc of glucose-saline is then given slowly at the rate of 20 to 30 drops per minute.

2) Concomitant with above fluids, a solution of 1000 cc of 5 per cent glucose in water is given through a second vein. To this solution is added 6 cc of 1 per cent neosynephrine or 4 mg. of norepinephrine. The rate that this solution is administered is determined by the patient's blood pressure response. The systolic blood pressure should be kept above one hundred by the neosynephrine solution, and the rate of flow gradually reduced as the blood pressure rises in response to the administration of saline and the

adrenal corticoids. In most cases, it will be possible to discontinue the neosynephrine solution within four hours after the initiation of salt and hormonal therapy. The subsequent electrolyte and fluid needs of the patient are determined by the clinical reaction, blood pressure, urinary output and serum electrolyte concentrations in accordance with plan outlined in Schedule 1.

Schedule III. An Alternate Schedule of Hormonal Therapy of Acute Adrenal Insufficiency

Ten cubic centimeters of lipo-adrenal cortical extract may be administered intramuscularly every hour for 3 doses. This is recommended by Dr. Herbert Kupperman as having greater latitude in dosage with less danger of precipitating pulmonary edema than if DCA is used.

Fifty cubic centimeters of aqueous cortical extract may be added to the isotonic saline infusion. If this material is not available intravenous solutions of cortisone or hydrocortisone may be used. The intravenous solutions are utilized more rapidly than intramuscular cortisone, thereby producing effects more promptly.

CONCLUSIONS

Acute adrenal insufficiency is a surgical hazard capable of causing death.

Surgical stress may precipitate acute adrenal insufficiency in patients previously unsuspected of having adrenal cortical inadequacy.

Effective preoperative and postoperative treatment may protect the patient from the crisis of hypo-adrenalism.

Tests for adrenal cortical function are available but it is not safe to assume that normal responses to such tests insure adequate cortical function necessary to cope with the stress of an operation.

There are no definite means to identify patients having adequate adrenal activity for uncomplicated life but which are incapable of providing sufficient corticoids to defend the body against severe stress.

In the event that unexplained shock develops following surgery which does not respond to the usual treatment, and a reasonable doubt arises that hypo-adrenalism exists, it is best to use appropriate therapy rather than withhold treatment. There is little reason to fear that such measures will be injurious even though they have been unnecessary in some instances.

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THE DIAGNOSIS OF HYDRONEPHROSIS BY PERCUTANEOUS RENAL PUNCTURE

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The radiologic diagnosis of hydronephrosis is usually adequately established by excretory or retrograde urography. There are, however, occasional cases in which for various reasons conventional radiographic procedures fail to yield satisfactory information.

It is the purpose of this paper to show that under these circumstances the diagnosis of hydronephrosis may be ascertained by direct renal puncture with injection of contrast medium into the dilated kidney pelvis or calyces. Our studies were stimulated by various reports describing the method of renal aspiration biopsy[1, 2] as well as by the work of Lindblom[3, 4] who advocated percutaneous renal puncture and injection of radiopaque media for the differential diagnosis of renal tumors and cysts.

The method of renal puncture will be briefly described and illustrative cases of hydronephrosis will be reported in which this procedure was utilized to advantage.

METHOD

Local anesthesia is usually employed although a general anesthetic might be given to young, apprehensive, or unco-operative patients. Suitable doses of barbiturates are administered one to two hours preceding the procedure to minimize procaine reactions. The patient is placed prone on a full length x-ray table and the entire middorsal region cleansed and prepared. An area just beneath the last rib on the suspected side and just lateral to the longitudinal muscles of the back is taken as the site for puncture. A skin wheal is raised with 1 per cent procaine solution and the abdominal wall infiltrated. In selected cases supplementary blockage of the lower intercostal nerves may be done. A 5 or 10 cc glass piston syringe attached to a 5 inch 18 gauge needle is used. If a mass is palpable the needle is directed towards the mass. Otherwise radiographic localization of the renal area should be performed with the patient in the prone position. Lead numbers on the patient's skin may serve as proper external landmarks.

When urine is obtained a small amount is aspirated for examination and contrast medium (20–30 cc of 35 per cent diodrast in this series) is immediately

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A markedly enlarged left kidney pelvis with very small calyces was detected (fig. 2). None of the contrast medium was seen to pass into the ureter or bladder.

On subsequent operation a large hydronephrosis due to ureteropelvic obstruction by a stricture with almost complete parenchymal destruction was discovered. A nephrectomy was performed. The convalescence was uneventful.

Comment: This 8 year old boy presented himself with a large mass in the left side of the abdomen. On cystoscopic examination the left ureteral orifice could not be detected. In order to avoid another cystoscopic instrumentation and general anesthesia it was considered less noxious to the patient to perform renal puncture. A large hydronephrotic kidney was demonstrated without difficulty and the patient withstood the procedure exceedingly well.

Case 3. T. E., a 42 year old Negro, was admitted to Grady Memorial Hospital in February 1953, with a diagnosis of urethral fistulas. Following a gonorrheal infection in 1934, a urethral stricture developed which required repeated instrumentations and several hospital admissions. In 1948 he suffered from a peri-urethral abscess which necessitated drainage.

Since that time multiple urethral fistulas had developed which extended into the perineum and persisted up to the present hospital admission.

On physical examination a large pelvic mass was detected which on barium enema was seen to elongate the rectum displacing it toward the right side. No intrinsic lesion of the rectum was recognized.

The laboratory findings indicated slight albuminuria. The urinalysis disclosed 14 to 16 red blood cells and 5 to 7 white blood cells per high power field. The other laboratory findings were not remarkable.

Excretory urography demonstrated right hydronephrosis and hydro-ureter. On immediate and delayed roentgenograms no excretion of contrast medium on the left side was detected.

In order to visualize the left upper urinary tract, a left renal puncture was performed and 30 cc of grossly purulent urine were obtained. Injection of 25 cc of 35 per cent diodrast made it possible to outline the left upper urinary tract. The kidney pelvis and several major calyces were found to be markedly distended. The entire ureter was tortuous and dilated. On upright tilting the contrast medium passed downward through the ureter to the level of the upper sacrum where a complete obstruction was encountered (fig. 3). None of the contrast medium passed into the urinary bladder. Several days later a left nephrostomy was performed which is still functioning at the present time.

Subsequently an advanced carcinoma of the urinary bladder was demonstrated, which apparently had caused obstruction of the left ureter.

Comment: In this patient multiple urethral fistulas and strictures did not permit retrograde pyelographic examination. Since, on excretory urography, the left upper urinary tract could not be outlined, renal puncture gave adequate information as to the appearance of the left ureter and kidney pelvis.

Case 4. R. M., a 47 year old Negro, was admitted to Grady Memorial Hospital in September 1952 because of epigastric pain, vomiting, weakness, poly-

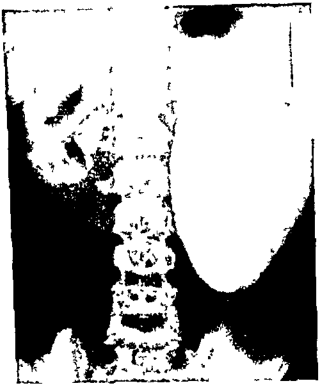

FIG. 2

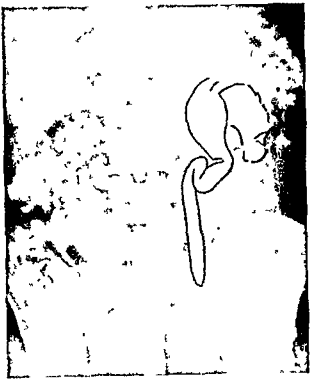

FIG 3

FIG. 2 Case 2 Huge hydronephrosis shown by renal puncture and injection of contrast medium.

FIG. 3. Case 3. Retouched. Marked dilatation of left upper urinary tract and ureteral obstruction demonstrated by renal puncture. Residual barium in colon shows large pararectal mass.

uria, and nocturia. His blood pressure was markedly elevated and there was evidence of moderate anemia. The laboratory findings indicated considerable nitrogen retention and the urinary excretion of phenolsulfonphthalein was not appreciable for a 2 hour period. A tentative diagnosis of chronic glomerulonephritis or chronic pyelonephritis was made and urologic consultation was requested to rule out an obstructive process of the urinary tracts.

Retrograde pyelography disclosed moderate left hydronephrosis probably due to ureteropelvic obstruction. On this examination it was not possible to introduce a catheter into the right ureter, nor could the right urinary tract be visualized by intravenous urography. On the following day under spinal anesthesia, another attempt was made to catheterize the right side but was again unsuccessful. An indwelling catheter was now placed into the left ureter to secure drainage of the left kidney.

Since the patient's clinical condition did not improve and he continued to have elevated temperatures, it appeared desirable to gain information about the right upper urinary tract. The right kidney pelvis was aspirated through the flank and 30 cc of grossly purulent material were obtained. After injection of 25 cc of 35 per cent diodrast, slight dilatation of the kidney pelvis and calyces and tortuosity and dilatation of the upper segment of the ureter became apparent (fig. 4). The opacified right ureter terminated abruptly at the level of the third lumbar vertebra but in follow-up films some of the contrast medium was noted to have passed into the urinary bladder. A right nephrostomy was then performed and on operation the entire ureter was found to be densely bound down by extensive inflammatory changes. The nephrostomy was removed in 8 weeks. In November 1952 a left pyeloplasty was carried out. The

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RENAL CHANGES IN PARAPLEGIA AS SCREENED BY ROUTINE EXCRETORY UROGRAPHY

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Experience has shown that one of the complications of spinal cord lesions is upper urinary tract involvement because of infection, calculosis, vesico-ureteral reflux and obstruction due to ureteral kinking associated with and without reflux.[1, 2, 3, 4, 5, 6] In order to evaluate the visible amount of pathological changes in the upper urinary tract, 315 pyelograms were screened for study at random. The purpose was to discover: 1) the general incidence of pathological changes irrespective of level and 2) to evaluate what part the following factors played in renal disease, a) the level of the spinal cord lesion, b) the completeness or incompleteness of the lesion, c) the time elapsed since the injury, and d) whether the right or left kidneys were affected more often.

Excretory urograms show both the anatomy and function of the kidneys; therefore, a routine was initiated whereby every patient underwent shortly after admission excretory urography and thereafter at yearly or even more frequent intervals. The patients periodically had blood urea nitrogen, nonprotein nitrogen, and phenolsulfonphthalein determinations, and retrograde pyelograms, when indicated, performed. Rogers and Bors[7] have reported their experience with tests of dilution-concentration, nonprotein nitrogen and phenolsulfonphthalein in paraplegia which dealt with the functional aspect of renal changes. It was believed that the excretory urograms supplied the best morphological information necessary for further studies.

In order to answer the questions put forth above, the excretory urograms of 315 patients were reviewed. Two hundred and eighty-nine patients had traumatic cord lesions, 171 of which were complete and 118 incomplete (tables 1 and 2). Twenty-six patients had either disease or tumor of the spinal cord of which 7 were complete and 19 incomplete.

CLASSIFICATION AND METHOD OF STUDY

In order to evaluate the findings, the following classification was used:

Grade 0 or N: Essentially normal pyelogram.

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TABLE 1. *Excretory urogram; statistics*

	COMPLETE LESIONS									INCOMPLETE LESIONS								
	Total Pts	R N	L N	R 1	L 1	R 2	L 2	R 3	L 3	Total Pts	R N	L N	R 1	L 1	R 2	L 2	R 3	L 3
Cervical	7	7	7	0	0	0	0	0	0	33	25	26	6	5	1	0	1	2
Dorsal 1–4	24	19	20	4	2	0	2	1	0	5	4	1	0	0	1	1	0	0
Dorsal 5–8	46	30	35	10	4	2	7	1	0	15	9	13	2	0	2	1	2	1
Dorsal 9–12	77	56	60	8	6	7	3	6	8	17	11	11	4	4	2	1	0	1
D-12, L-1	4	2	2	0	0	0	0	2	2	5	5	5	0	0	0	0	0	0
Lumbar	13	5	7	2	2	6	4	0	0	13	31	33	7	6	2	3	3	1
Grand total	171	119	131	24	14	15	16	13	10	118	85	92	19	15	8	6	6	5
Disease or Tumor	7	3	3	1	2	2	2	1	0	19	11	16	3	2	2	1	0	0

Tabulation presents percentage of normal and pathological kidneys broken down according to various level groups among traumatic spinal cord lesions and also presents results found among nontraumatic cord lesions in group of pyelograms that were graded.

Numerals in vertical columns under heading "total" refer to number of patients' pyelograms graded in each category of neurological levels. All other figures are percentages.

From these percentages figure 1 was created

TABLE 2. *Excretory urogram; percentages*

	COMPLETE LESIONS									INCOMPLETE LESIONS								
	Total Pts.	R N	L N	R 1	L 1	R 2	L 2	R 3	L 3	Total Pts.	R N	L N	R 1	L 1	R 2	L 2	R 3	L 3
Cervical..........	7	100	100	0	0	0	0	0	0	33	75.7	78.7	18.1	15.1	3	0	3	6
Dorsal 1–4........	24	79.1	83.3	16.6	8.3	0	8.3	4.1	0	5	80	80	0	0	20	20	0	0
Dorsal 5–8........	46	65.2	76	21.7	8.6	4.3	15.2	8.6	0	15	60	86.6	13.3	0	13.3	6.6	13.3	6.6
Dorsal 9-12.......	77	72.7	77.9	10.3	7.7	9	3.8	7.7	10.3	17	64.7	64.7	23.5	23.5	11.7	0.8	0	5.8
Dorsal 12, L-1....	4	50	50	0	0	0	0	50	50	5	100	100	0	0	0	0	0	0
Lumbar...........	13	38.4	53.8	15.3	15.3	46.1	30.7	0	0	43	72	76.7	16.2	13.9	4.6	6.9	6.9	2.3
Grand total.....	171	69.5	76.0	14.0	8.1	8.7	9.3	7.6	5.8	118	72	76.2	16.1	12.7	6.7	5.0	5.0	4.2
Disease or tumor.	7	42.8	42.8	14.2	28.5	28.5	28.5	14.2	0	19	76.6	84.2	15.7	10.5	10.5	5.2	0	0

Tabulation presents number of right and left kidneys with their respective grades (normal or pathological). It is broken down according to vertebral level groups or disease or tumor group.

Grade 1: a) Mild blunting of minor calyces, or
b) Mild dilatation of major calyces, or
c) Mild dilatation of renal pelvis, or
d) Combination of the above.
Grade 2: a) Moderate to marked calyceectasis, or
b) Moderate to marked pyelectasis, or
c) Moderate to marked retention of dye, or
d) Combination of above.
Grade 3: a) Gross hydronephrosis.

Although overlapping of grades admittedly occurs, the practical value appears adequate and satisfactory, especially since the evaluation was performed by the author and therefore all films were read similarly.[4]

In order to study the relationships such as time since injury and completeness or incompleteness of the lesion against the various levels of injury, the factors were plotted graphically. Figures 2 and 3 are presented as an example of the largest number of patients in any one respective level.

ANALYSIS

I. General incidence of pathological changes. Six hundred and thirty kidneys were graded. Irrespective of level, completeness of lesion, time since injury and type of spinal cord lesion it was found that: 467 kidneys or 73 per cent were graded as N; 76 or 12 per cent were considered as grade 1; 52 or 8 per cent were grade 2; and 35 or 6 per cent were grade 3. From these figures one then can estimate the number of pathological findings at any given time though there will be some fluctuation.

On examining whether a difference of incidence exists between the traumatic cases and those with disease or tumor irrespective of level, one finds that there is no difference in cases with incomplete lesions, whereas in cases with complete lesions pathological changes are more frequent with the disease or tumor group than with the traumatic group.

II. Incidence of pathological changes.

a) General incidence of pathological kidney changes with regard to vertebral level in traumatic lesions: Figure 1 shows that there is a definite increase in the number of cases with renal disease among patients with a lumbar or D12–L1 level.

This confirms the author's clinical impression that patients classified[1, 2] as having a lower motor neuron type of bladder show more pathological change; the conus medullaris is usually damaged in these cases (D12–L1 and lumbar vertebral levels). Among the causative factors of kidney damage, calculosis and infection are the most common and perhaps also vesico-ureteral reflux, although this is a more frequent event with upper motor neuron lesions.[3]

b) Incidence of pathological kidney changes in relation to the completeness or incompleteness of the spinal cord lesions: Figure 1 reveals that there is no marked difference of incidence in the cervical and dorsal groups, in regard to the completeness of the lesion. However there is a difference in the D12–L1 group and

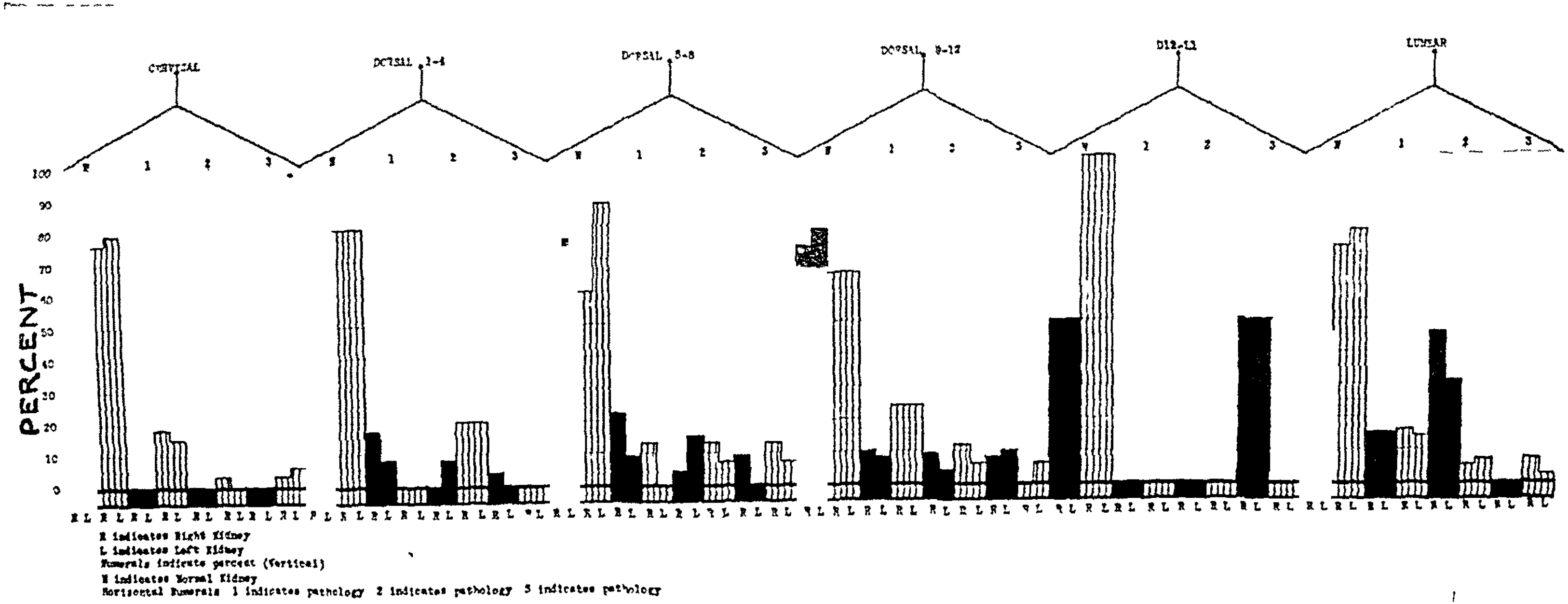

FIG. 1. Depicting percentage (vertical numbers on left) of normal kidneys (N), grade 1 pathological change kidneys (1), grade 2 pathological change kidneys (2), and grade 3 pathological kidneys (3) found in traumatic cord lesions according to vertebral level groups.

Complete (solid dark shaded vertical columns) and incomplete (nonsolid light shaded columns) refer to spinal cord lesion.

Figure graphically shows percentages listed in table 2 (traumatic lesions only).

TABLE 3

Complete lesions

	RIGHT KIDNEY							LEFT KIDNEY						
	Oldest Normal	Earliest #1 Pathology	Oldest #1 Pathology	Earliest #2 Pathology	Oldest #2 Pathology	Earliest #3 Pathology	Oldest #3 Pathology	Oldest Normal	Earliest #1 Pathology	Oldest #1 Pathology	Earliest #2 Pathology	Oldest #2 Pathology	Earliest #3 Pathology	Oldest #3 Pathology
Cervical	50							50						
D1–4	55	3	47			28		59	3	46	28	19		
D5–8	68	2	56	45	150	49	97	97	21	59	29	150		
D9–12	74	8	56	23	132	35	174	174	8	54	23	19	39	132
D12–L1	63					52	64	63					52	64
Lumbar	100	34	42	8	77			100	23	42	54	77		
Dis or tumor	51	88		10	96	18		51	18	88	40	96		

Incomplete lesions

	RIGHT KIDNEY							LEFT KIDNEY						
	Oldest Normal	Earliest #1 Pathology	Oldest #1 Pathology	Earliest #2 Pathology	Oldest #2 Pathology	Earliest #3 Pathology	Oldest #3 Pathology	Oldest Normal	Earliest #1 Pathology	Oldest #1 Pathology	Earliest #2 Pathology	Oldest #2 Pathology	Earliest #3 Pathology	Oldest #3 Pathology
Cervical	73	6	47	34		59		57	12	84			10	59
D1–4	56			51				56			51			
D5–8	51	23	364	13	52	28	52	52			364		28	
D9–12	60	48	57	9	21			60	9	57	21		48	
D12–L1	65							65						
Lumbar	79	4	48	46	60	16	71	79	4	60	46	71	16	
Dis or tumor	372	2	35	27	51			372	26	35	27			

An attempt is made to demonstrate when pathological change of each grade first appears and how long after injury do we still find normal appearing kidneys This is further divided into the various levels and whether the neurological lesion is complete or incomplete All numbers indicate *time in months*.

the lumbar group, in that the pathological changes were greater with complete than with incomplete lesions. The reason for this may be the fact that patients with incomplete lesions are more active physically, including ambulation.

c) Incidence of pathological kidney changes in relation to the time element: The earliest time of detection of a grade number 1 was 2 months after injury; the earliest date of observation of a grade number 2 change was 8 months after injury; and the earliest notice of a grade number 3 change was 10 months after injury. There is, therefore, a relationship between the time which has elapsed since injury and the degree of the pathological change. However, this trend does not indicate that the pathological change takes place at that respective date of necessity, because grade 1 was seen as late as 364 months, grade 2 after 150 months, and grade 3 after 174 months. Neither does it imply that changes must take place eventually, since normal kidneys were observed as late as 372 months after trauma (table 3).

d) Comparison of pathological changes in right and left kidneys: The pathological changes in right and left kidneys were as follows:

	RIGHT KIDNEYS						LEFT KIDNEYS					
	Complete			Incomplete			Complete			Incomplete		
Degree of pathology	1	2	3	1	2	3	1	2	3	1	2	3
No. of kidneys	25	17	14	19	10	6	16	18	10	16	7	5
Degree of pathology			1	2	3				1	2	3	
Total No. of kidneys			44	27	20				35	25	15	

It is interesting that the right kidneys showed somewhat more frequent pathological changes than the left. It is also worth mentioning that among six nephrectomies performed during this period, five concerned the right side and that among the 56 patients studied at this Center with vesico-ureteral reflux, 25 cases had bilateral while 19 had right and 12 left reflux; this again points to the right kidney.[3]

DISCUSSION

"More damage to the upper urinary tract occurs in patients whose bladders function poorly."[4] This statement may be slightly too dogmatic, although it has didactic merits for the rehabilitation of cord bladders. In order to explain our point we quote an example from our experience: A patient who had an adequate transurethral resection and alcohol subarachnoid block shortly after injury developed an excellent lower motor neuron type of bladder[1, 2] with 0 residual; yet, bilateral vesico-ureteral reflux and bilateral hydronephrosis developed. We have frequently encountered upper motor neuron bladders, which despite excellent balance developed pathological renal changes. And last, but not least, even patients who were on straight drainage with an intra-urethral catheter, who arrived from another hospital and in whom no attempt has yet been made to create an automatic bladder, developed within the short post-traumatic period of a few months reflux with grade 2 changes. In brief, desirable as it is to attain

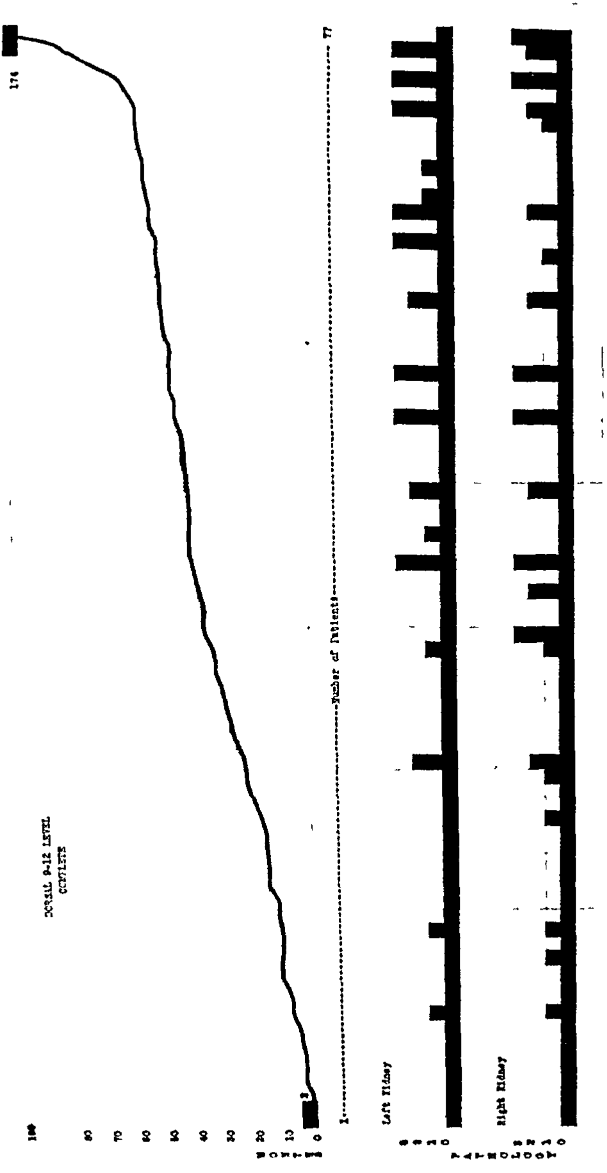

FIG. 2. Effect of time against pathological change found in both right and left kidneys in traumatic group level between dorsal 9–12. Lesions are neurologically complete. Solid vertical black bands represent amount of pathological change. Each block running horizontally represents a patient.

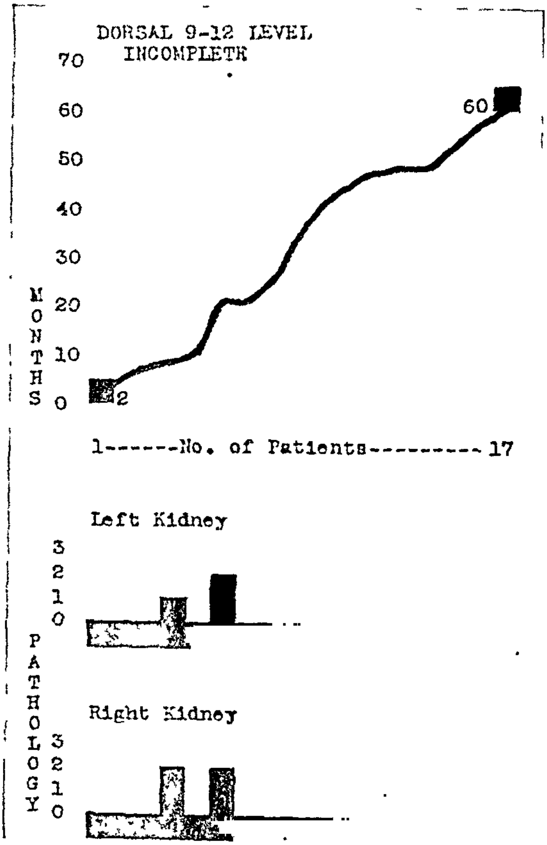

FIG. 3. Similar to figure 2 except that these are incomplete lesions in levels dorsal 9-12.

the goal of a well balanced cord bladder, this *per se* is no assurance that the kidney will stay healthy.

Thus it is impossible to prognosticate the future of kidneys in neurogenic bladders by judging the bladder function alone; this is illustrated by a patient who had a good automatic bladder after 174 months and whose right kidney was a grade 3 lesion whereas the left kidney was normal (fig. 2). Nevertheless it is evident that the time factor plays an important part in increasing the chance for kidney damage (fig. 2).

Six cervical patients in this group had suprapubic catheters, and their kidneys were normal except in one patient who was graded as 1. This corroborates our general clinical impression that most patients with well functioning suprapubic cystotomies are free from frequent pyelonephritic sieges even in the presence of vesico-ureteral reflux. This significant observation will require additional attention and further study.

SUMMARY

The excretory urograms of 315 patients were graded according to a scale which ranged from normal to grade 1, grade 2 and grade 3.

Two hundred and eighty-nine patients had traumatic cord lesions; 26 patients had tumors or a disease of the spinal cord.

Among the evaluated 630 kidneys irrespective of level, completeness or type of cord lesion, and time since injury, 467 kidneys (73 per cent) were essentially normal; 76 kidneys (12 per cent) were graded as grade 1 (mild degree of change); 52 kidneys (8 per cent) were graded as grade 2 (moderate degree of change); and 35 (6 per cent) were graded as grade 3 (severe degree of change, hydronephrosis).

The incidence of pathological changes of the kidney increases with lower lesions.

Pathological changes of the kidney are rather independent of the extent of the cord lesion.

Pathological changes of the kidneys tend to increase with the time elapsed since injury. The earliest grade 1 was seen two months; the earliest grade 2 eight months; and the earliest grade 3 ten months post-injury.

The function of a cord bladder per se does not determine necessarily the future of the kidneys.

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A BACTERIAL CALCULUS IN THE RENAL PELVIS

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A bacterial calculus in the renal pelvis is a rare but interesting finding. This case is the second of its kind in the history of St. Peter's Hospital; the first was reported by Ward in 1926.

CASE REPORT

A woman aged 60 first attended St. Peter's Hospital in September 1952. Her main symptom was pain in the right loin for 6 months. It was of typical renal distribution radiating from the loin down into the groin. There was no frequency of micturition and hematuria had never been noted. She had had two operations on her right kidney in 1910 for renal calculus.

Examination of the patient showed her to be in good general condition. Her cardiovascular, respiratory and nervous systems were normal for her age. An operative scar was noted in her right loin. Both kidneys were palpable. Blood urea was 34 mg. per cent. The following was the report on the examination of urine: Albumin and pus present, film shows numerous gram negative bacilli; on culture there is a profuse growth of B. coli. Excretion pyelography showed both renal shadows to be enlarged, the left one was due to functional hypertrophy. No excretion was visible on the right side but the left kidney was normal in function and structure. No opaque calculus was seen.

The operation of right nephrectomy was performed September 19, 1952. The old scar in the loin was excised. A very adherent kidney was exposed. It was removed but there was considerable difficulty in mobilizing the kidney. The wound was closed with the tube drainage. The kidney was not incised in the operating theater because it is the practice at St. Peter's Hospital to fix all kidneys for three to four days in formalin solution. At the end of that period they are opened by the pathologist, Dr. Cuthbert Dukes.

Convalescence was uneventful and the patient was discharged home 13 days after the operation.

Pathologist's report (Dr. Cuthbert Dukes): The kidney was slightly enlarged, weighed 210 gm. and measured 10 cm. in its long axis. The outer surface was normal except in the region of the junction of the upper and middle thirds, where there was a depressed scar, the site of a previous operation. When the kidney was opened (fig. 1) a very unusual condition was revealed. The renal pelvis was occupied by a solid structure which appeared to be a calculus but was soft and putty-like in consistence and could be easily cut with a knife. It is visible in the photograph as a dark structure in the renal pelvis.

Microscopic examination showed this to be a bacterial calculus composed of masses of gram negative bacilli. The tests for calculi showed the material to be

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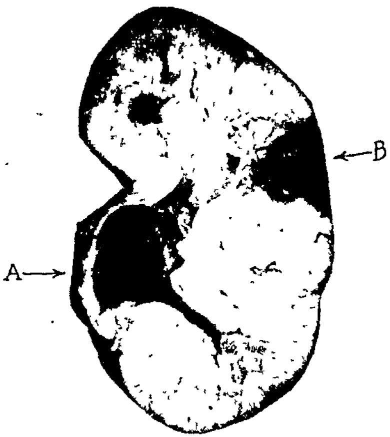

FIG. 1. *A*, bacterial calculus in renal pelvis. *B*, hemorrhage due operative trauma.

organic in character. When sectioned and examined microscopically it was seen to be composed of clusters of bacteria surrounded by and enclosed in a coagulated and fibrinous exudate. The kidney itself was unusual in appearance. In the middle third it was pale in color and no normal markings were visible. Sections from this region showed an advanced stage of chronic pyelonephritis and fibrous tissue replacement with extensive patches of calcification. The dark patch visible at the junction of the upper and middle thirds was hemorrhage due to operative trauma.

COMMENT

Kelly and Dible agree that these cases are rare. They believe that the following conditions are necessary for these calculi to form: 1) some sort of nucleus about which the concretions grow; 2) some cementing process which causes the mass to adhere; 3) circumstances which favor their retention in the renal pelvis during the early stages of their formation.

Although the 3 cases reported by Hyman were all of bacterial calculi in the bladder following suprapubic prostatectomy, he states that they are found more often in the kidney. In his opinion the diagnosis is seldom established before operation. This may be due to the fact that they are not radio-opaque.

Scholl in reporting two personal cases says "continous infection seems necessary."

The patient of Ward passed over a hundred bacterial calculi before operation. The calculi were so soft that they had an easy passage down the ureter. He does not know what factor—"caused the bacteria to cohere and form these very numerous concretions, whilst in other patients infected with the same organism only a bacilluria or urinary infection results."

In presenting this case report I should like to lay emphasis on the value of preserving kidneys after removal for three to four days in formalin solution before examining them. I believe that had this kidney been incised in the operating theater the calculus might have been mistaken for a blood clot and so an interesting pathological specimen would have been lost. It was the observation that the calculus was cut so easily with a knife which raised the query that it might be a bacterial calculus.

SUMMARY

A case of a bacterial calculus in the renal pelvis is reported.

A plea is made for the preservation of removed kidneys for three to four days in formalin solution before dissecting them.

This case was shown at a meeting of the Urological Section of the Royal Society of Medicine and I wish to thank the Council for permission to publish the case. In addition I beg to acknowledge the valuable help I received from Mr. Harland Rees and Dr. Cuthbert Dukes in the preparation of this article.

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RENAL PAPILLARY NECROSIS: A CLINICOPATHOLOGIC STUDY

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The scarcity of papers in the urologic literature dealing with renal papillary necrosis has prompted the submission of this report. A revival of interest in renal papillary necrosis followed Gunther's report[1] in 1937 correlating this pathologic entity with diabetes mellitus. Mandel[2] has recently summarized the numerous case reports, few of which were diagnosed clinically. At the Indiana University Medical Center, 6 cases of renal papillary necrosis have been recognized since 1945; two of the patients survive and four are deceased. These 6 cases form the basis of this study.

INCIDENCE

As summarized by Mandel in 1952, 160 cases have been recorded in the available literature since 1877, when first described by von Friedreich.[3] Ninety-six of these cases were associated with diabetes mellitus, whereas 64 were apparently nondiabetic. Obstruction of the urinary tract was present in 63 and absent in 97. It is significant that only 16 had neither diabetes mellitus nor urinary tract obstruction. In two series of autopsied diabetics, the incidence of papillary necrosis has been 3.37 per cent and 4.75 per cent.[4, 5] In these series of diabetics about one fourth succumbing to acute pyelonephritis have had papillary necrosis. The incidence of this entity in urinary tract obstruction is so small that no accurate statistics have been established.

Female diabetics are prone to have papillary necrosis twice as frequently as their male counterparts, whereas in nondiabetics the males outnumber females six to one. This incidence is presumably due to the greater incidence of urinary obstruction in men. The majority of both diabetic and nondiabetic patients with this lesion are over 50 years of age. The lesion was bilateral in 61 of 160 cases reviewed by Mandel.

DIAGNOSIS

Renal papillary necrosis must be suspected in any diabetic with severe acute pyelonephritis, gross hematuria, renal colic, micturition of solid material, or rapidly progressive renal insufficiency not responsive to chemotherapy and diabetic management. The disease may be an acute, fulminating, rapidly fatal process, or it may be relatively chronic and progressive, with or without intermittent or terminal acute, fulminating episodes.[2, 4, 5, 6, 7] Oliguria and anuria may occur. The severity of the diabetes does not seem to be a factor.[5]

Accepted for publication January 21, 1954.

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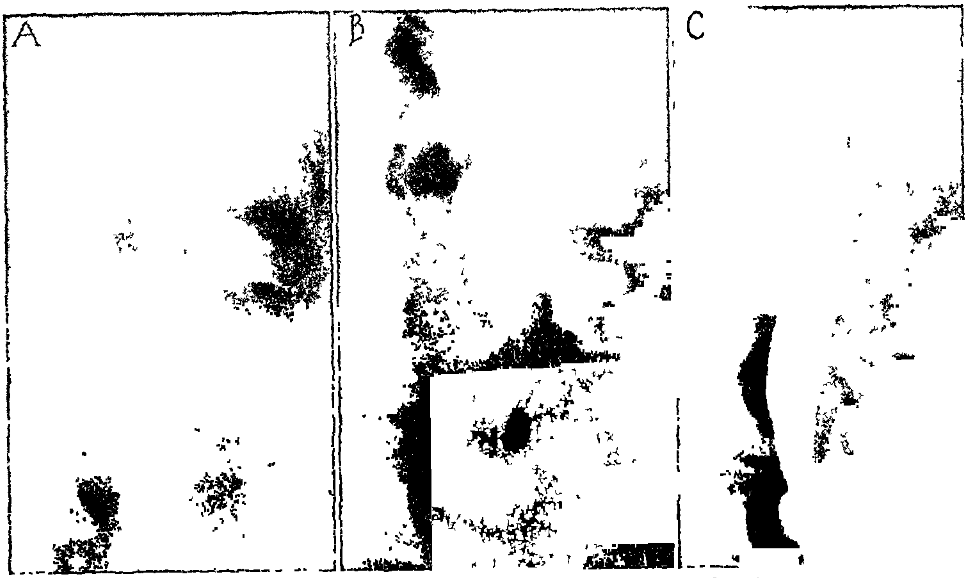

FIG. 1. *A*, case V. C. "Ring shadow" is evident in superior calyx in left retrograde pyelogram. Papilla lies separated in calyx. *B*, case V. C. Six weeks following A, sloughed papillas leave clubbing on left. *C*, case M. W. Late results as noted by pyelography of left kidney 2 weeks before death. Note both clubbed and ragged calyces. Cortical abscesses also found at autopsy.

Gross hematuria may denote the slough of a papilla. The line of separation between necrotic papilla and viable medullary parenchyma is the site of hemorrhage. Hematuria is often severe, with the passage of vermiform clots.

Renal colic indicates obstruction of a major calyx or ureter by sloughed parenchyma or by blood clot. Obstruction may exist to a high degree.

The passage of a papilla in the urine is of course a dramatic event. This is a rather rare phenomenon, many such masses either being overlooked or undergoing liquefaction necrosis prior to their excretion. Such solid masses that are passed and submitted to the physician are conclusive evidence when examined microscopically.

More difficult of identification are those diabetics whose renal function progressively fails. Many diabetic patients with pyelonephritis in whom papillary necrosis is not found will tend to follow this fatal course. Only an omnipresent awareness of the possibility of such a necrotic reaction will bear diagnostic fruits.

Roentgenographic study must often be utilized. The retrograde pyelo-ureterogram may be helpful, if not diagnostic. Early changes noted are those of ragged irregularities reminiscent of renal tuberculosis,[8] usually selective of one or two minor calyces. Later, separation of the papilla will leave a "ring shadow" in the calyx (fig. 1, *A*). A negative filling defect within the pelvis indicates the passage of the papilla into the collecting system. The calyx, deprived of its papilla, displays a clubbed appearance not unlike that seen in hydronephrosis. In this clubbing, however, pelvic dilatation is not found. It should be emphasized that the so-called "ring shadows" and pelvic defects due to loose papillae at pyelography are extremely uncommon. In pyelographic studies more frequently one notes end-results of sloughing. Here typically are seen clubbed minor calyces in the absence of obstruction. Many such patterns are overlooked, simple pyelonephritis being advanced as the diagnosis. These findings are illustrated in figure 1, *B* and *C*.

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The clinical diagnosis of papillary necrosis in the nondiabetic is an even more difficult problem because of its relative rarity. Only familiarity with the typical roentgenographic picture and careful histologic study of tissue fragments submitted by the patient will lead to the diagnosis. The vast majority of these cases, diabetic or nondiabetic, reach the autopsy table before papillary necrosis is suspected.

CASE REPORT

A 43-year-old white housewife was admitted to the Indiana University Medical Center for the first time on November 17, 1951 with complaints of nausea, vomiting, and mild malaise for 2 weeks. The patient was a known diabetic, taking insulin and a diabetic diet. One month before admission a diagnosis of pyelonephritis was made by her local physician, and a series of furuncles was reported 2 weeks later. Known hypertension of 4 years' duration was the only other significant feature of this history. The physical examination was entirely normal except for a blood pressure of 158/90.

Significant laboratory studies included a urine concentration of 1.010 with a faint trace of albumin and 3 plus pyuria. Hemoglobin was 9 gm. with 3.01 million red cells. White cell count and differential were normal. The admission nonprotein nitrogen was 55 mg. per cent; phenolsulfonphthalein tests revealed 13 per cent excretion in 15 minutes, and a total of 31 per cent in 30 minutes. Escherichia intermedium was obtained on urine culture. Fasting blood sugar was 250 mg. per cent. Excretory urography demonstrated no visualization, and retrograde pyelography revealed a filling defect in the left pelvis with blunting of the calyces. The

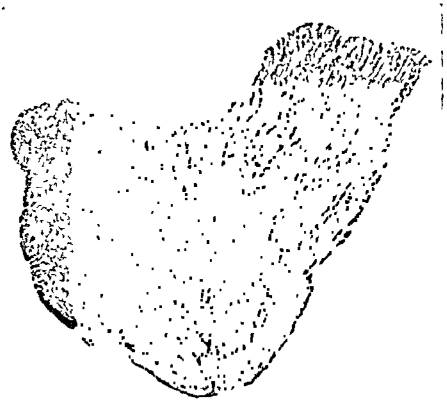

FIG. 2. Case V. C. (S.P. 64767). Low power. Necrotic papilla recovered from urine

patient was placed on terramycin and made a satisfactory response prior to discharge.

The patient was followed in the clinic, and made satisfactory progress except for intermittent episodes considered to be pyelonephritis with left renal colic. Antibiotic therapy was used intermittently. On April 15, 1952, the patient reported passing a small piece of tissue in the urine and brought this specimen to the clinic. She was subsequently re-admitted on April 17, 1952 with the tentative diagnosis of papillary necrosis. In addition, she reported a recent history of gross hematuria. Physical examination was unchanged except for blood pressure of 180/95. Again the urine showed a faint trace of albumin and pyuria. Her diabetic control was entirely satisfactory. Retrograde pyelography demonstrated left hydronephrosis, and subsequent films led to the diagnosis of papillary necrosis.

The specimen passed by the patient consisted of two pieces of tissue which were grayish-white and friable. The larger measured 2.0 by 1.0 by 3.0 cm. and the smaller about 5.0 mm. Microscopically the sections showed a necrotic papilla in which the outline of tubules was visible (fig. 2).

Again the patient was given antibiotics and made a satisfactory response prior to discharge. As an out-patient, she continued to report bouts of frequency, burning, gross hematuria and, for the first time, right flank pain. Antibiotics were used intermittently, and on July 28, 1952 the patient was re-admitted. She appeared acutely ill and complained of severe right flank pain necessitating narcotics. Temperature was 103F, and marked right costovertebral angle tenderness was present. Blood pressure was 76/42. The blood sugar was essentially normal; CO_2 combining power was 21 m/Eq., nonprotein nitrogen was 65 mg. per cent. Albuminuria, pyuria, and hematuria were again noted. A right ureteral obstruction was relieved by catheterization. She received terramycin, penicillin, and symptomatic care; again she made a satisfactory response and has been followed as an out-patient, remaining asymptomatic.

ETIOLOGY

The appearance of the lesions of papillary necrosis is that of infarction of the papilla, with or without superimposed infection. The pyramids derive their blood

FIG. 3. Case M. N. (S.P. 41083). Gross appearance of cross section of kidney showing necrotic papilla partially detached.

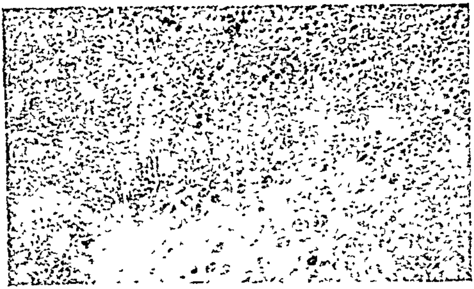

FIG. 4. Case E. R. (autopsy 12151). Low power. Sharp line of demarcation between viable and necrotic tissue. Note capillary thrombi in viable portion.

supply from branches directly from the arcuate arteries. Vessels arising as continuations of efferent arteries from the juxtamedullary glomeruli (Trueta shunt) may also be present. These vessels are susceptible to occlusion by pressure as well as thrombosis in certain disease states. Occlusion of these vessels does not impair the blood supply to the columns of Bertini or the cortex, and these structures are spared in papillary necrosis.

In necrotizing papillitis, occlusion of the vessels supplying the pyramids may be brought about in several ways, as evidenced by clinical and experimental studies. Multiple thrombi in vessels of the pyramids are occasionally seen in human cases, and were produced in a dog and in rabbits by Mandel and Popper[9] by the injection of vinylamine. In many human cases, multiple thrombi are absent.

The compression of vessels by inflammatory edema may be an important mechanism in the production of these lesions. Most patients with papillary necrosis have acute pyelonephritis, in many instances to a severe degree. The photomicrographs of reported cases and our own material reveal a marked degree of edema accompanying the inflammatory reaction. The causative organism probably is not important except for the degree of edema it excites. The organisms reported include Klebsiella pneumoniae, streptococci of the viridans type, tubercle bacilli, and actinomyces, but Micrococcus pyogenes var. aureus and Escherichia coli have been encountered most frequently. The role of the lowered pH suggested by Edmundson,[4] citing the work of Menkin, may be important in that it helped increase the edema.

That other vascular diseases of the kidney, such as arteriolonephrosclerosis and intercapillary glomerulosclerosis, play a role in the development of these lesions is suggested by their frequent occurrence in reported cases. The already-embarrassed circulation would appear to be more susceptible to further insult.

The presence of para-amyloid in some cases of papillary necrosis was assigned a significant role by Mellgren.[10] Here again, a taxed blood supply was probably more susceptible to added injury.

Obstruction of the urinary flow has been important in clinical cases, especially

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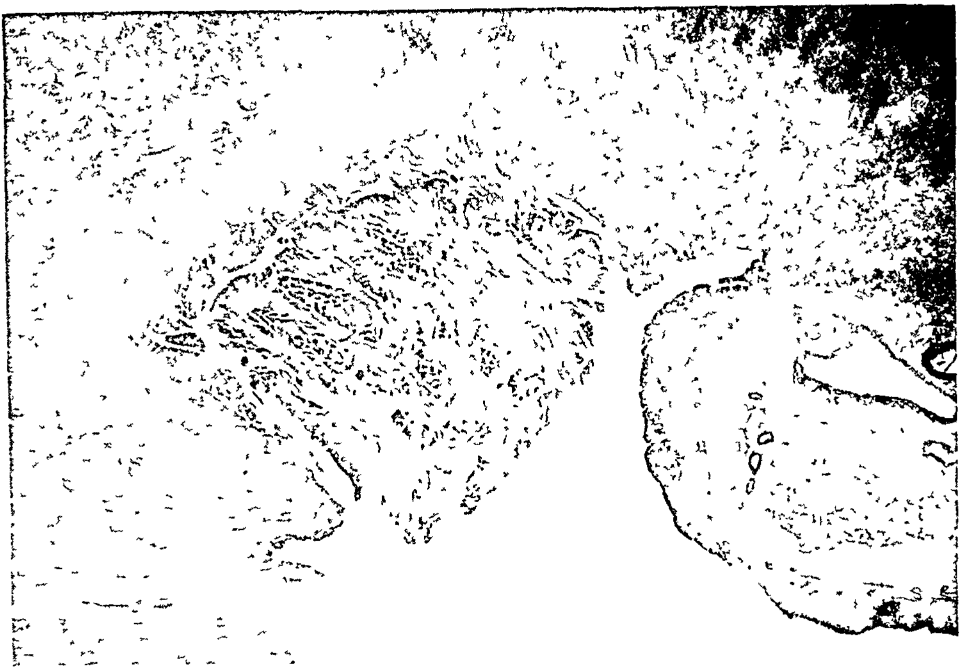

FIG 5 Case M. N (S P 41083) Low power Almost complete separation of necrotic papilla This stage would be represented as "ring shadow", as noted in figure 1, *A*

in nondiabetic males. Muirhead[11] felt that the increase in intrapelvic pressure produced in his animals (dogs) was sufficient to occlude the medullary vessels, with the development of necrotizing papillitis. In human cases obstruction not only raises the intrapelvic pressure but also potentiates infection.

PATHOLOGY

The degree of papillary necrosis varies in the same kidney and from case to case. There may be necrosis of the entire papilla (fig. 3) or part thereof. Frequently, even when only a part of the papilla is involved, the necrosis extends from the base to the tip, and usually located laterally. The necrosis is of the coagulative type, and there is a sharp line of demarcation at the junction with viable tissue (fig. 4) Grossly the necrotic part may be yellow, green, or dark red. Occasionally there are capillary thrombi along the border of necrosis (fig. 4); usually there is edema of the interstitial tissue; less frequently there is cellular infiltration. As the lesions progress, the necrotic zone sequestrates, the line of cleavage being a sharp one starting at the lateral border of the base of the papilla and working centrally, so that the last point of juncture is usually in the midportion (fig. 5). The columns of Bertini remain uninvolved. As the papilla separates, the interstitial tissue at the base is infiltrated with wandering cells, especially plasma cells and lymphocytes. When the separation is complete the border is sharp (fig. 6, *A*). The necrotic papilla lies free in the pelvis (fig. 6, *B*). In addition there may be varying degrees of arterio- and arteriolar sclerosis, and pyelonephritis. Abscesses are frequently, but not always, present (fig. 6, *B* and *C*).

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[11] Muirhead, E E , Vanatta, J and Grollman, A · J A M A , **142**: 627, 1950

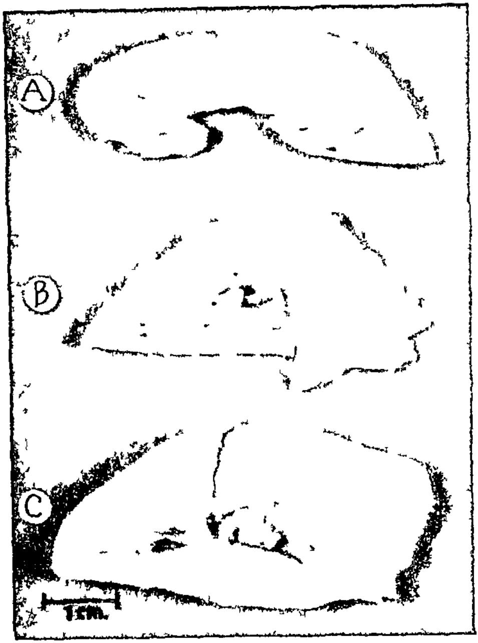

FIG 6 Case M W (autopsy I 3035) Gross appearance of kidney on cross section showing varying stages *A* appearance after papilla has been sloughed leaving clean line of separation This would be represented as clubbed calyx as noted in figure 1, *B* and *C* *B* and *C*, partially separated papillae are evident Abscesses of the kidney are present

MANAGEMENT

There is a paucity of published information on the management of papillary necrosis To be sure, infection is the dominant and immediate problem at hand It must be emphasized that careful bacteriologic studies of the offending organisms are imperative These should include drug sensitivity tests with *all* the available antibiotics Inasmuch as the rapidity of renal destruction is often alarming, potent antibiotic therapy must be brought to bear promptly

Enhancement of existing renal infection as well as hydronephrotic destruction of renal parenchyma must be avoided Blockage of the drainage channels with sloughed tissue may be a serious problem, ureteral catheter drainage may suffice temporarily Irrigation of the pelvis and ureter with streptokinase streptodornase may cause rapid lysis of the sloughed tissue Surgical intervention for obstruction unrelieved by such conservative methods may conceivably be necessary

Nephrectomy has been advocated and may be life saving However, careful consideration of medical management, the exclusion of the existence of bilateral disease, and evaluation of total renal function, must precede any decision for

TABLE I

Case	V C	E R.	M W.	H. H.	M. N.	D. P.
Age	43 years	21 years	50 years	48 years	58 years	78 years
Sex	Female	Female	Female	Female	Female	Female
Diabetes duration	9 years	14 years	2 months +	1 year	Unknown	None
Daily insulin requirements	30 units	80 units	13 units	*Unknown*	25 Units	—
Urinary obstruction	No	No	No	No	No	Bilat
Hypertension	Yes	No	No	No	No	No
Azotemia	Yes	Yes	Yes	Yes	Yes	Yes
Hematuria	Yes	Yes	Yes	Yes	Yes	Yes
Pyelonephritis	Yes	Yes	Yes	Yes	Yes	Chronic
Bacteria	E intermedium, E. coli	E coli, non hemolytic streptococci	Hemolytic streptococci., P. vulgaris, Staph aureus	Hemolytic streptococci., A. aerogenes, E. freundii	Unknown	Unknown
Bacteremia	E coli	E coli, hemolytic streptococci	No	E. coli	Unknown	Unknown
Other renal disease	*	†	†	‡	Unknown	—
Diagnosed	Tissue from urine	Autopsy	Autopsy	Autopsy	Surgical specimen	Autopsy
Unilateral or bilateral	Bilat (?)	Bilat.	Bilat.	Unilat.	Unilat.(?)	Bilat.
Duration to death	Living 1½ years later	2 months	4 weeks	5 weeks	Living 2 years later	Unknown

* Pyonephrosis (last admission)

† Intercapillary glomerulosclerosis

‡ Hypoplasia of one kidney

extirpation of renal parenchyma Effective antibiotic therapy may eliminate or postpone nephrectomy Certainly nephrectomy is contra-indicated if the integrity of the opposite kidney is in question

DISCUSSION

Our 6 cases (table 1) closely parallel those previously reported All demonstrated dysuria, hematuria, chills, fever, nausea, and vomiting Four of the six reported characteristic renal colic Three showed porstration and stupor, and two were in coma It is interesting to note that all but one were diabetic females without urinary tract obstruction, and that the severity of their diabetes, as measured by the daily insulin requirements, varied from 13 to 80 units per day Four of the patients were in the 40 to 60 year group, whereas one was only 21 years old, the latter being younger than those generally reported The diagnosis of acute pyelonephritis was made in all cases, and the organism or organisms were established in four In three, bacteremia was confirmed by blood culture In contrast with some reports, hypertension was found in only one patient The presence of concomitant renal disease is noteworthy Two of the four patients studied at postmortem examination had intercapillary glomerulosclerosis

Bilateral papillary necrosis was confirmed in three patients and unilateral involvement in one In the fifth, it was assumed but unproven that the disease was unilateral, whereas x-ray evidence was conclusive of bilateral disease in the sixth Four of our patients manifested the typical fulminating and rapidly fatal course of this entity, but it is perhaps significant that two of them are living and apparently well 1½ and 2 years later

In one of our cases, reported in detail, the diagnosis was established antemortem by histological study of tissue obtained from the urine We have found only five similar cases in the literature

Careful consideration of the sequence of pathogenesis is the key to pyelographic diagnosis in this lesion Ragged calyces, ring shadows, and clubbing of the calyces all have their counterpart in pathologic material

SUMMARY

Papillary necrosis must be suspected in diabetics with severe renal infection or renal failure

The diagnosis can be confirmed by histologic examination of sloughed tissue or pyelographic studies showing ring shadows Ragged or isolated clubbed calyces are strongly suggestive of this lesion

Nephrectomy in the acute unilateral disease may be beneficial In bilateral disease, diabetic control, antibacterial therapy and promotion of free urinary drainage are the only courses of action available

Six cases of papillary necrosis are herein reported, one in detail

The photographs were prepared by Mr James F Glore of the Department of Illustration

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CONGENITAL SOLITARY PELVIC KIDNEY. A STUDY OF ITS BLOOD SUPPLY BY AORTOGRAPHY

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The principal anatomical features which distinguish the congenital ectopic kidney from the ptosed kidney, i.e. a kidney that has wandered from its normal place, are its short ureter and the low origin of its blood supply. These vessels may originate from the lower few inches of the aorta or from the large vessels in the true pelvis.

Ectopic kidneys have been classified by their position. Eisendrath and Rolnick (1938), for instance, divided them into the following groups: 1) low lumbar, between normal position and the fifth lumbar vertebra; 2) iliolumbar, across the crest of the ilium; 3) iliac, in the iliac fossa; 4) iliopelvic, at the level of the brim of the true pelvis; 5) pelvic, within the true pelvis.

Transitional types have also been encountered. Judging by the literature some workers have included the iliac or iliopelvic kidney in the group of "solitary pelvic kidney".

A solitary pelvic kidney is very rare. According to Stevens (1937) it is met with once in approximately 22,000 autopsies. Beneventi (1950) collected 43 cases from the literature and added a case of his own. We have traced a further 21 cases in the literature which, together with the case now presented, bring the total number of reported cases to 66 (table 1).

An understanding of the blood supply of the ectopic kidney rests on the knowledge of renal embryology. The kidneys appear first in the true pelvis as two buds, which arise from the wolffian ducts and the distal parts of the wolffian bodies. They form the metanephros at this stage. During the process of development the kidneys migrate upwards. A temporary blood supply is received from the internal iliac artery, common iliac artery, neighboring vessels or from the aorta. The permanent blood supply is not acquired until the kidneys have reached their normal position, which occurs at the end of the second month of intra-uterine life when the embryo is in the 25-30 mm. stage. If the kidneys do not migrate upwards or their ascent is arrested, the temporary blood supply then becomes the permanent one. The origin of the vascular supply of the ectopic kidney shows great variety.

CASE REPORT

Hospital record No. 727/52, a girl, aged 16 years, sought medical advice because of amenorrhoea. Otherwise the past history was irrelevant. The attending physician discovered a mass in the true pelvis, which he suspected to be a hematometra secondary to aplasia of the vagina, and referred the patient to our clinic for treatment.

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FAILURE OF FREEZE-DRIED HOMOLOGOUS ARTERIES USED AS URETERAL GRAFTS

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Homologous arteries preserved by freeze-drying have been used successfully for bridging arterial defects[1, 2] in dogs. The cells of the graft are dead, but the noncellular elements persist for a long period of time and function mechanically until the graft is adequately replaced by invading fibroblasts of the host. The graft is well accepted and shows less foreign body reaction than is expected from a comparable fresh homograft. Freeze-dried tissue, in contrast to a viable graft, has no living cells to contribute to the fibroblastic reaction and scar formation. The muscle cells degenerate very rapidly, but the collagen persists for several months, and the elastic fibers remain for many years.

Freeze-dried homologous arteries used as a sheath around injured tendons prevented fixation of the tendon to surrounding tissues by adhesions.[3] Freeze-dried homologous dura was used successfully for replacing dural defects[4] and freeze-dried fascia, for defects of the abdominal wall.[5]

At the time the present project was designed, it appeared that freeze-dried arteries or veins might be well tolerated as replacements for ureters. The chances of success seemed good if the grafts could be adequately replaced by host fibroblasts, and if a mucosal lining would grow in from the ends of the host ureters.

METHOD

Eight centimeter segments of carotid artery and jugular vein were removed from dogs at sterile autopsy. They were frozen at −68°C and dried directly from the frozen state in a vacuum of about 50 microns of mercury pressure. They were sealed *in vacuo* in small ampules and stored for several weeks at room temperature. The grafts were reconstituted by immersion in a sterile saline solution for 30 to 45 minutes.

Ten recipient dogs were used in the project. A 10 cm. segment of the left ureter was removed from each dog through a transperitoneal approach. The defect was replaced by an 8 cm. segment of preserved carotid artery in 5 dogs. In the other

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The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

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* Present address: Albany Hospital, Albany, N. Y.

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five, similar replacement of the defect by a segment of jugular vein was attempted

Anastomoses were done with 6-0 chromic catgut or 6 0 arterial silk as an over and over or everting mattress suture Individual sutures were placed about 0 5 mm apart, and it was usually possible to obtain watertight suture lines

During the first two attempts to insert the vein grafts, technical difficulties arose because the veins were considerably larger than the ureters In the remaining 3 dogs, the ureter was dilated by placing wire clips just above the trigone two or three days prior to the grafting Although adequately dilated, these ureters were so thin that leakage through the suture holes was uncontrollable, and two of the 3 dogs in which this dilation was produced were the only ones in which a watertight insertion of the graft could not be accomplished No attempt was made to insert a splint in the ureter, and the abdomen was closed without drainage Antibiotics were not given

RESULTS

Implantation of vein grafts was technically unsuccessful in two of the dogs in the series One dog with a vein graft died 3 weeks postoperatively from peritonitis secondary to leakage from the suture line The remaining 2 dogs with vein grafts and all of the five with arterial grafts were sacrificed at postoperative intervals, varying up to 10 weeks

Gross observations revealed massive destruction of the inner layers of the grafts In some animals, mucosa grew for a short distance around the outside of the graft in the connective tissue bed, but in no case did it grow along the inside In several dogs, there was a 1 to 3 cm pocket outside a suture line but in communication with the lumen of the ureter These pockets were filled with urine which had forced its way along the outside of the graft and raised it from its bed Strictures at the suture lines were formed in nearly all dogs Hydroureter and hydronephrosis developed early in all of the dogs, and in some cases were demonstrated by excretory urogram as early as the fifth day postoperatively.

DISCUSSION

The dilatation of the proximal ureter probably was due to the absence of peristalsis in the graft with resulting functional obstruction Judging from other work[6] [7] this might be expected in any type of long, nonliving, or synthetic prosthesis

The stricture formation at the suture lines might have been prevented by the insertion of catheters or vitallium tubes However, this maneuver would not have prevented disintegration of the graft before it could be replaced by fibroblasts from the host The fact that a very delicate atraumatic suture line adequately prevented stricture formation in a small visceral tube such as the common bile duct[8] suggests that the suture technique itself was not a primary cause of failure

Failure of these ureteral grafts might have been predicted on the basis of more recently available information describing the failure of homologous ureter,[9] and of autogenous artery and vein in the ureter.[9, 10]

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[7] Narath, P A Renal Pelvis and Ureter New York Grune and Stratton, Inc , 1951

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This project and our recent study of freeze-dried arterial grafts for replacement of the common bile duct and esophagus[11] illustrate an important basic observation in the use of freeze-dried tissue. The chances of permanent success are greatly diminished in the presence of bacterial contamination or irritating chemicals.

Plastic[9] and metal tubing[12, 13] have been used for bridging defects in the ureter with some success, but have been complicated by encrustation and migration of the tube. Probably the most successful methods at the present time are those using segments of the patient's own bowel.[14, 15]

SUMMARY AND CONCLUSIONS

Homologous carotid arteries and jugular veins preserved by the freeze-drying process were used to fill 10 cm. defects in the ureters of 8 dogs. These grafts failed because of disintegration of the graft without host replacement and stricture formation at the suture lines.

This failure is in contrast to the results obtained when freeze-dried homologous arteries were used for bridging arterial defects, and as sheaths for preventing the formation of adhesions around injured tendons. Freeze-dried homologous dura successfully filled dural defects, and freeze-dried fascia replaced defects in the fascia and muscle of the abdominal wall.

The failure of the grafts in the ureters is similar to the results obtained with freeze-dried artery in the common duct, and in the esophagus. They illustrate a basic observation in the use of this type of graft. The chances of success are greatly diminished in the presence of bacterial contamination or irritating chemicals.

The author wishes to express appreciation for the skilled operating room management and surgical assistance by S. T. Scott, HM2, USN; R. L. Replogle, HM2, USN; and W. E. Dunham, HM2, USN. Students from the Tissue Bank School of the Naval Medical School assisted during the procedures.

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A DEVICE FOR THE MANAGEMENT OF CUTANEOUS URETEROSTOMY

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No method of urinary diversion has proved ideal and cutaneous ureterostomy certainly provides its share of disadvantages from the standpoints of social inconvenience and upper urinary tract complications. There is strong likelihood, however, that every urologist will on some occasion find it necessary or advisable to do cutaneous ureterostomy either as an emergency or as an elective operation. When this procedure has been carried out, one of the following methods of management is commonly employed: 1) an indwelling catheter, 2) some type of cup, 3) a catheter in conjunction with a cup.

Aside from the desires of the patient certain situations dictate the need for a catheter type of management.

1) A catheter, either alone or in combination with a cup, must be used if there is a noncorrectible stricture of any portion of the ureter or if the ureter and/or pelvis are irreversibly decompensated as a result of past obstruction-infection with consequent urinary retention in the upper tract. The latter can be determined very readily by catheterization of the renal pelvis for residual urine after a 24 hour period without an indwelling catheter.

2) A catheter must be used when the use of a cup is impractical by virtue of the position of the ureteral stoma, adjacent scar preventing adhesion of a cup, marked obesity, skin sensitivity to the cup or to the cement, etc.

Although it is, of course, possible to use a catheter type of management in the patient without stricture or upper tract residual urine, the advantages of avoiding the insertion of a foreign body with the consequent hazards of infection and stone formation make the use of a cup the method of choice, from the urologic standpoint, in the management of such cases. Experience has demonstrated that patients properly selected for the cup type of management may retain architecturally and functionally normal kidneys for periods of many months or years without clinical evidence of urinary tract infection.

DESCRIPTION OF DEVICE

To circumvent certain of the disadvantages of the Singer cup,[1] the authors in conjunction with the United Surgical Supply Co.,* devised the cup illustrated in figure 1. The cup consists of a separate flange (I) and cap (II), made of pliable rubber, which combine (III) to form a watertight unit. The flange has a starting hole in the center which may be tailored with scissors to fit the shape and size of the stoma up to a diameter of 1¼ inches. The cap is provided with tabs for

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* United Surgical Supply Co., Mamaroneck, N. Y.

[1] Trafton, H. M. and Kaufman, M.: J. Urol., 58: 159, 1947.

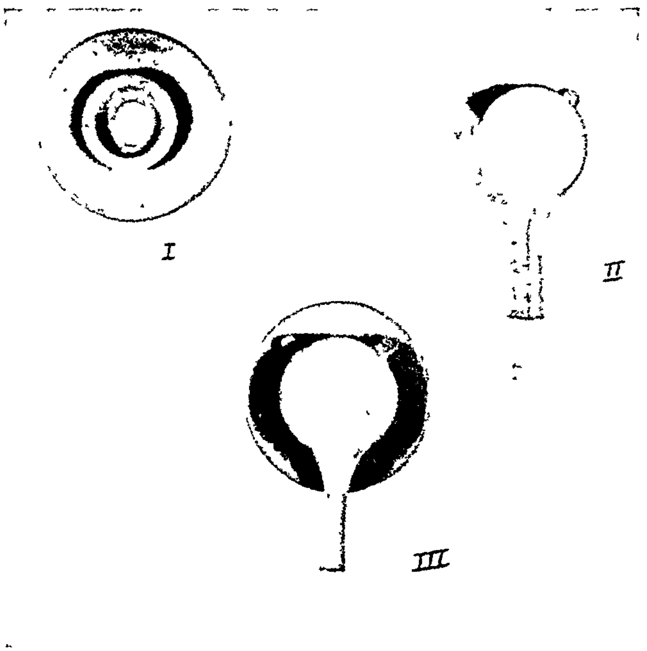

FIG. 1

easy adjustment of the cap to the flange. Similar in general principle to the Singer cup, the separation of cap and flange, which constitutes the major innovation in this device, has three practical advantages:

1) It simplifies and improves the reliability of application of the cup. 2) It permits the patient to cleanse the ureteral stoma daily without the need for detaching the flange from the skin. 3) It permits the patient to relieve the negative pressure which may develop beneath the applied cup by temporarily breaking the seal by gentle traction on one of the rubber tabs on the cap of the cup.

TECHNIQUE OF APPLICATION OF DEVICE

A. Technique of application of cup alone:

1) Shave all hair within radius of 5 cm. of ureterostomy.

2) Cleanse the skin and ureterostomy with soap and water, and dry.

3) Apply compound tincture of benzoin with an applicator to the cleansed skin and allow to dry. While doing this, hold a gauze square or facial tissue, rolled cigarette fashion, over the ureteral stoma to absorb urine and keep the skin dry.

4) Using a finger or rubber mucilage brush, spread a thin coating of cement evenly on the flange of the cup and set aside to dry.

5) With the rolled gauze or facial tissue over the ureteral stoma use finger or rubber mucilage brush to apply cement to skin around the ureteral stoma over an area corresponding with the flange of the cup.

6) Slip the flange of the cup over the gauze square or facial tissue onto the prepared area of skin and hold firmly in place for about five minutes.

7) Hold the cap rim under the flange ridge and gently pull the cap over the ridge until it snaps into place The drainage tube on the cap should point downward

8) Connect the drainage tube appropriately to a rubber urinal Plastic spiral rings can be conveniently utilized to prevent kinking of tubing

9) To remove the flange, simply peel it off the skin The skin cement is readily removed by rubbing or with the aid of ether The cement on the flange should not be removed on each occasion since the thick rough coating seems to improve adhesive qualities Patients are ordinarily advised to remove the flange at least once a week

B Technique of application of cup in conjunction with catheter

1) Soft plastic catheters are preferable but rubber may be used

2) Insert catheter up ureter to renal pelvis in the usual way At the properly calibrated level, mark catheter with nail polish Determination of the proper distance of insertion may be accomplished by careful irrigation but is most accurately done by suitable roentgenograms

3) Prepare flange and skin as previously described, eliminating use of gauze, etc

4) When cement on skin is dry, slip flange over catheter and hold firmly in position for about 5 minutes

5) Insert small safety pin through catheter at previously marked position

6) Cut catheter just above pin and apply cap

7) When catheters and cups are used in combination, the patient is advised to remove the caps twice daily and the flange at least once a week

No matter what the method of management, the following procedure is recommended for night drainage

1) Leg urinals are removed and straight bilateral drainage is instituted with expendable plastic drainage tubing connected from cup to drainage bottle

2) To minimize the negative pressure in the cup at night a 3½ inch needle may be inserted in each expendable drainage tube at mattress level The air vent thus provided has been found helpful in preventing irritation of the skin adjacent to the ureteral stoma caused by negative pressure from the otherwise unbroken column of urine As a further aid in preventing this siphon effect, the distal end of the drainage tube should be so anchored at the drainage bottle that it cannot reach below the level of the accumulating urine

DISCUSSION

This cup, either alone or in conjunction with a ureteral catheter, has been employed in more than thirty patients with unilateral or bilateral cutaneous ureterostomies at Memorial Center during the past year and has proved an effective method of management Properly applied cups can ordinarily be relied on to keep the patient clean and dry for three to seven days in spite of a normally wide range of occupational and recreational activities By cutting a somewhat larger hole in the flange, it has also been used successfully[7] in the manage

[7] McGinnis, G F Personal communication

ment of the Bricker[3] type of artificial bladder and could conceivably be adapted for use with other types of "ostomies" if desirable.

SUMMARY

A device which has been found useful in the management of cutaneous ureterostomies is presented and the techniques of application outlined.

The authors wish to express their thanks to Mr. Jack Blackwood of the United Surgical Supply Co. whose interest and ingenuity led to the development of this device.

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VESICOURETERAL REFLUX IN CHILDREN

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In 1951 an operative procedure designed to correct vesicoureteral reflux in paraplegic patients was described by one of us.[1] A question was raised as to the applicability of this operation to the correction of the reflux encountered in children. In an effort to answer this question our study was undertaken. It includes 8 children each of whom had persistent vesicoureteral reflux, hydroureter and hydronephrosis to varying degrees, and clinical symptoms consisting for the most part of recurring episodes of urinary tract infection and kidney pain. In all, 14 ureters were subjected to the operation. All but one of the cases has been followed from three to four years.

The operation has been described elsewhere.[1] Briefly it is an attempt to increase the length of the intravesical segment of the ureter. It is accomplished by dissecting the intramural ureter from its attachments to the bladder wall except at the trigone. After this has been done a 2 cm. segment of ureter is pulled into the bladder and the defect in the bladder wall created by the dissection of the intramural ureter is sutured under the newly created intravesical ureter.

CASE REPORTS

Case 1. J. H., a 9 year old girl, was born with a meningomyocele. At the age of 11 months she had many white blood cells in her urine and was already showing left hydronephrosis and reflux up the dilated left ureter. The meningomyelocele was removed surgically at the State University of Iowa Hospitals in 1946. She was seen in February 1950, on the urology service because of pyuria, chills and fever. Her examination revealed hydronephrosis, hydroureter, calyectasis and reflux bilaterally. On July 27, 1951, a plastic operation was performed on the left ureterovesical junction.

A checkup examination on February 22, 1952, seven months postoperatively, revealed that she had been clinically well since her operation except for two episodes of chills and fever, each of which was controlled easily by gantrisin. Her cystogram demonstrated reflux up the right ureter but the reflux of the left ureter was no longer present. Excretory urograms revealed excellent function in 5 minutes bilaterally and the films were essentially unchanged as compared with the preoperative excretory urograms.

This child has been carefully followed at 6 month intervals during the ensuing 3½ years. Repeated delayed cystograms have failed to demonstrate any reflux up the left ureter. Excretory urography on March 7, 1955 revealed excellent function of the left kidney in 5 minutes and appeared essentially identical with the films taken 7 months postoperatively. Clinically, the child has done well. A marked reduction has resulted in the episodes of chills and fever and those that have occurred have been less severe than before the operation. See figure 1.

Read at annual meeting, American Urological Association, Los Angeles, Calif., May 16-19, 1955.

[1] Hutch, J. A.: Vesicoureteral reflux in paraplegics. J. Urol., 68: 457, 1952.

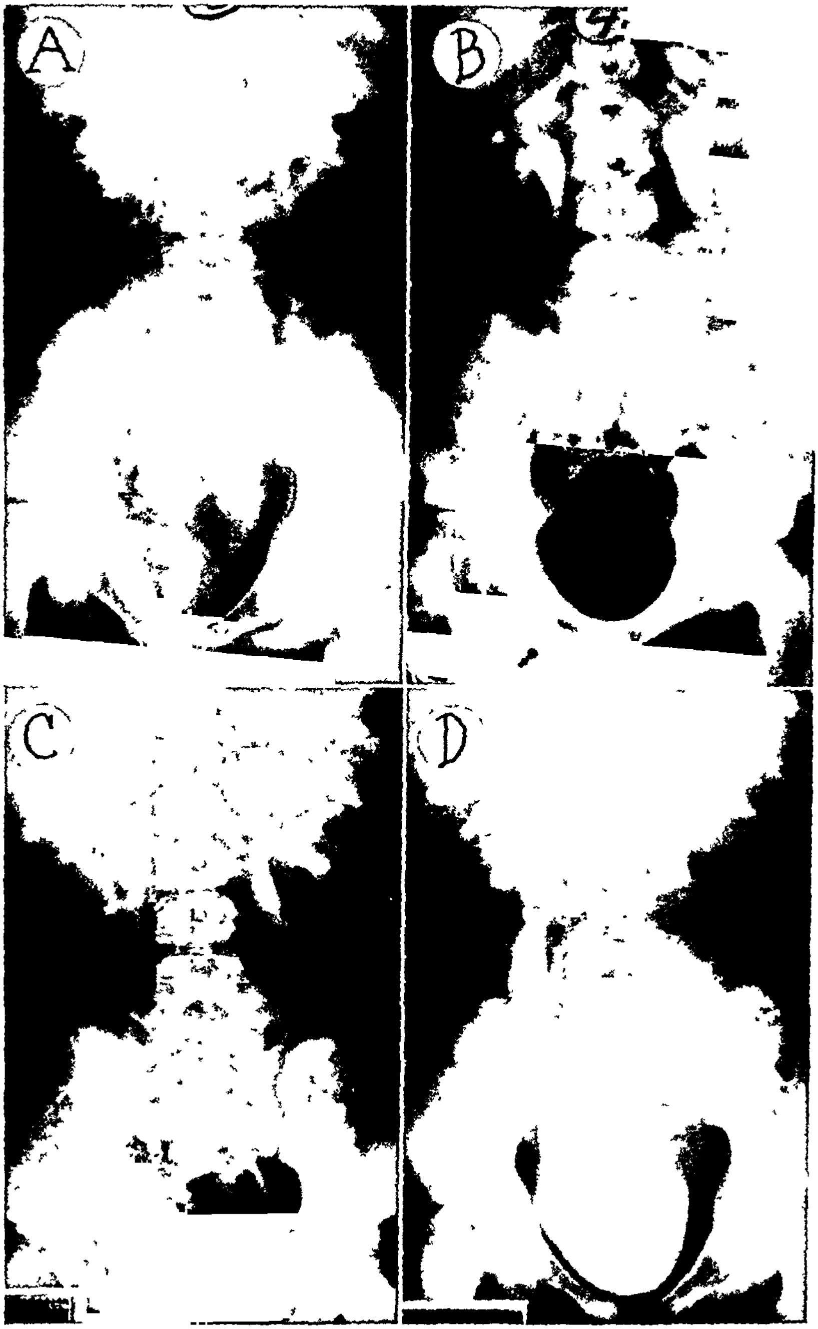

FIG. 1. Case 1. *A*, preoperative excretory urogram. *B*, preoperative cystogram. *C*, excretory urogram 7 months postoperatively. *D*, cystogram 7 months postoperatively.

The fate of the unoperated right ureter has not been good. Reflux has continued into this ureter and progressive dilatation has occurred. Recently it became necessary to do a plastic operation at the right ureterovesical junction in an effort to prevent further deterioration of the right kidney. While this operation stopped the reflux up the right ureter, the function of the right kidney remains poor, the ureter and the renal pelvis remain dilated and emptying from the right ureter is slow

Case 2 S L, a 3½ year old boy, was born with a meningomyelocele At the age of 13 months it was removed surgically in the State University of Iowa Hospitals He had neurological disturbance in his right foot and wore a brace Urologically, this patient had incontinence of urine and repeated episodes of chills, fever, pyuria and left flank pain His rectal tone was zero and his feces had to be manually extracted Cystograms revealed complete left reflux with hydroureter, hydronephrosis and calyectasis Excretory urograms showed an essentially normal right upper urinary tract except for a right re duplicated ureter On the left, no diodrast was seen until 15 minutes after injection and it appeared in puddles outlining the calyces A left vesicoureteral plasty was done on August 24, 1951

A checkup examination on November 26, 1951 (three months postoperatively) revealed that the boy had been improved clinically Since his operation he had had no more chills or fever or abdominal pains His cystogram revealed no reflux up either ureter Excretory urography demonstrated good function bilaterally in 5 minutes with a definite improvement in the left kidney to a point where normal calyceal cupping can be seen

This child has been followed carefully since operation Delayed cystograms have failed to reveal any recurrence of the left reflux Repeated excretory urograms have been normal The chills and fever and pain in the left flank have disappeared and according to his father, the only symptom remaining is the urinary incontinence See figure 2

Case 3 M C, a 9 year old girl, was born with a meningomyelocele She was first seen at the State University of Iowa Hospitals in 1948, at which time her right kidney was nonfunctioning Severe hydroureter and hydronephrosis were present and reflux occurred up the right ureter The left kidney had good function and appeared normal by excretory urography The right kidney was removed She has been followed carefully since and has had left flank pain, especially when voiding She is incontinent of urine and has marked pyuria with occasional chills and fever In November 1951, excretory urograms revealed good function of the solitary left kidney with mild dilatation of the renal pelvis Cystograms revealed reflux up the stump of the right ureter and complete left reflux A plastic operation was done on the left ureterovesical junction on November 15, 1951 Postoperatively the patient did well and 2 weeks later the reflux was no longer present Excretory urography revealed excellent function in 5 minutes, but calyectasis and hydronephrosis were more marked than preoperatively

Followup examinations failed to show any recurrence of the reflux but excretory urography demonstrated a slow dilatation of the remaining kidney Two and a half years postoperatively it was necessary to do nephrostomy to preserve this patient's life See figure 3

Case 4 K H, a 6 year old white girl, was a difficult foot presentation at birth and was delivered by cesarian section Immediately after birth a deformity of the left foot was noted and treatment begun in the orthopedic department of State University of Iowa Hospitals Bowel and bladder control never developed

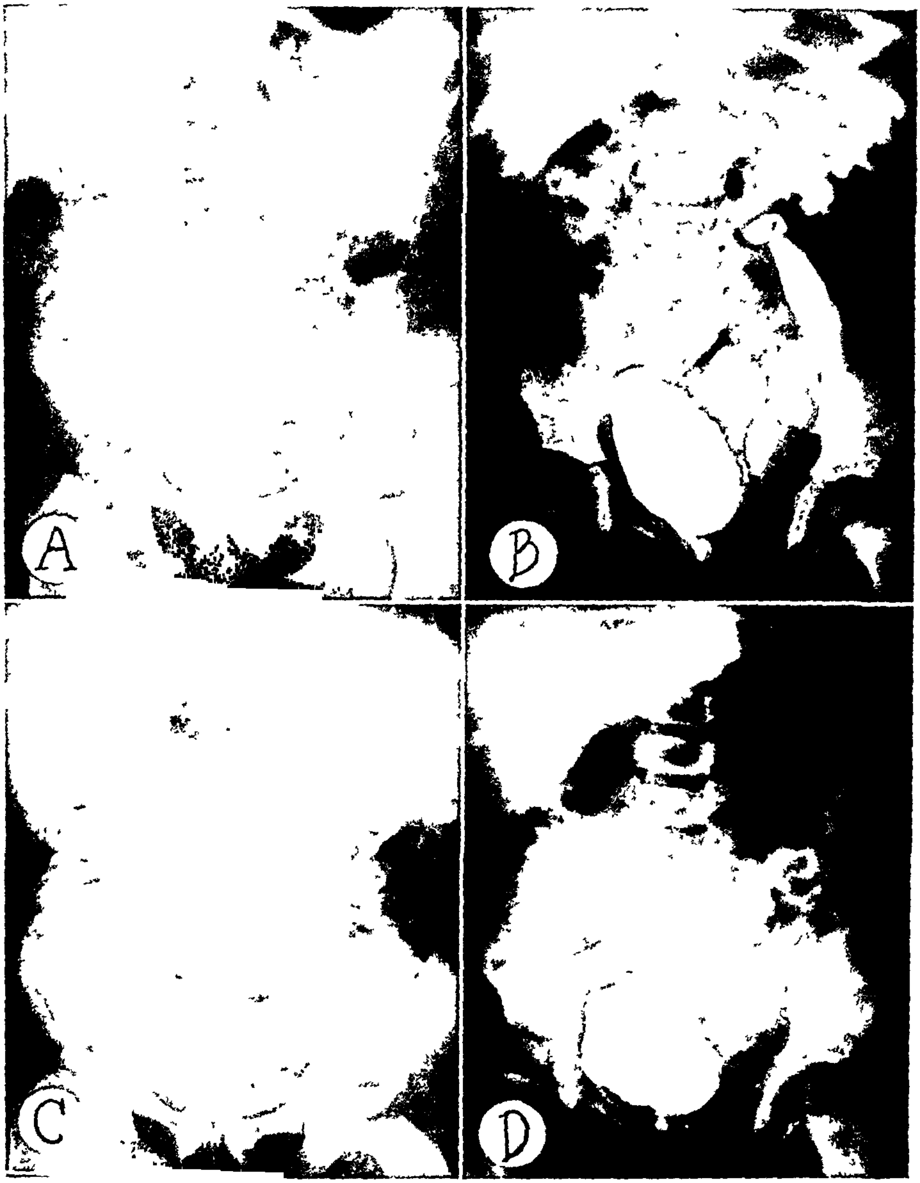

FIG. 2. Case 2. *A*, preoperative excretory urogram. No contrast medium seen on 5-minute film on left side. In 15 minutes dye appeared in puddles in region of left kidney, as is outlined. *B*, preoperative cystogram. *C*, excretory urogram 3 months postoperatively. Function present in 5 minutes and calyceal cupping has returned. *D*, cystogram made 3 months postoperatively.

At the age of four, examination in another hospital revealed bilateral hydroureter, hydronephrosis and ureteral reflux. Through the patient's life, episodes of chills and fever and bilateral flank pain have occurred on an average of once every two months. These have been controlled with chloromycetin.

Physical examination revealed atrophy of the left foot, no anal sphincter tone and constant dribbling of urine. Cystoscopically, a saccule was demonstrated at each lateral boundary of the trigone and the respective intramural ureter passed

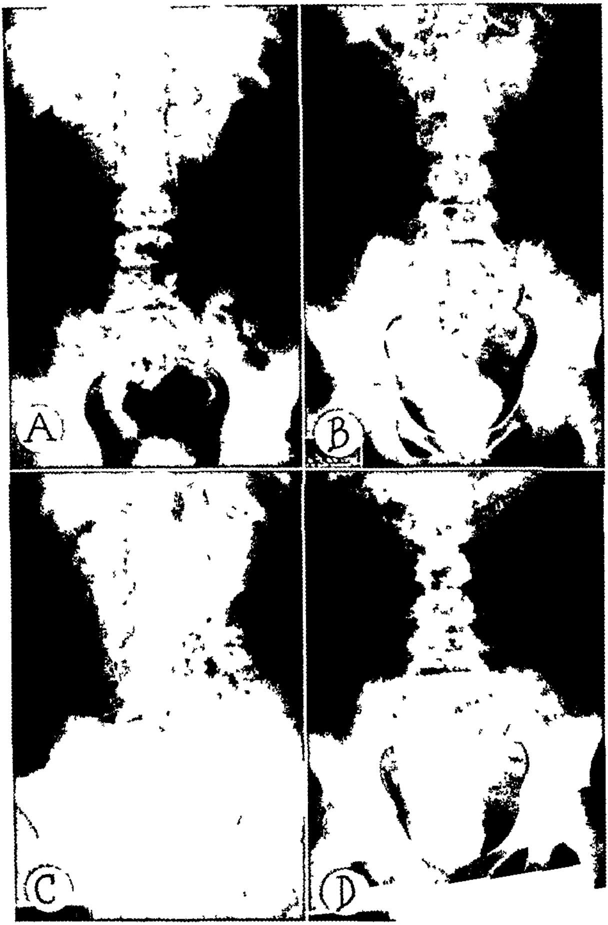

Fig 3 Case 3 *A*, preoperative excretory urogram *B*, preoperative cystogram showing reflux into stump of right ureter and complete left reflux *C*, postoperative excretory urogram shows increased dilatation of left kidney Dilatation slowly progressed and nephrostomy necessary 2½ years later *D*, postoperative cystogram

along the floor of each saccule. Excretory urography showed good function bilaterally with marked bilateral hydronephrosis and calyectasis Cystograms demonstrated severe bilateral ureteral reflux On August 10, 1951, a vesicoureteral plasty was done on the right side

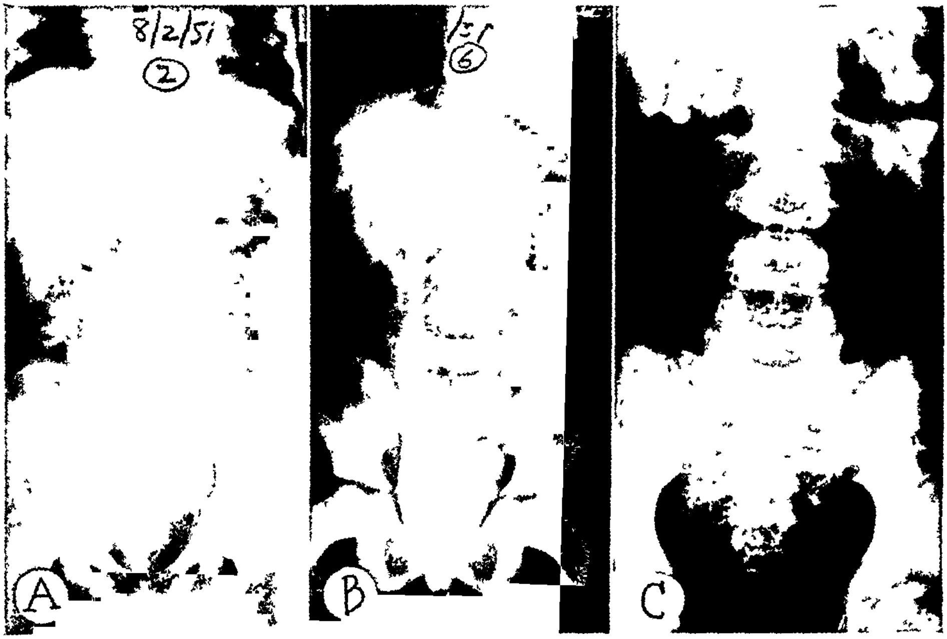

FIG. 4. Case 4. *A*, preoperative excretory urogram. *B*, preoperative cystogram. *C*, excretory urogram 2½ years after plastic operation on right ureterovesical junction and 1½ years after similar operation at left ureterovesical junction.

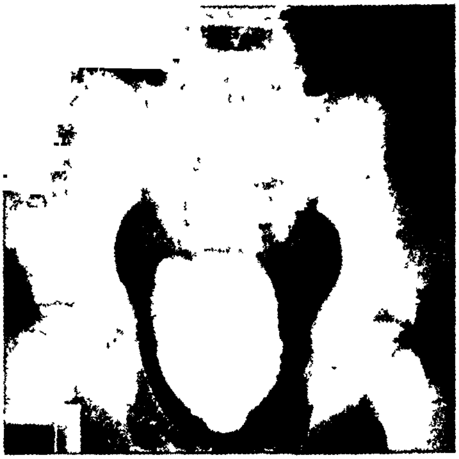

FIG. 5. Case 4. Cystogram made at time described in figure 4, *C*

A cystogram made 3 weeks postoperatively revealed reflux on the left, but none on the right. The excretory urogram was unchanged from the preoperative one.

Followup examinations were so satisfactory that a vesicoureteral plasty was done on the left 1 year later. She continued to do well and her examination on March 4, 1954 (two and a half years postoperatively on the right and 1½ years postoperatively on the left) revealed no reflux into either ureter. The excretory urograms were quite satisfactory and were improved over the preoperative ones. Clinically, the patient was enjoying the best health of her life, according to her mother. Her urine was free of infection. We were quite encouraged at this point.

However, examination 6 months later showed an increase in dilatation of the upper urinary tract bilaterally Examination in February 1955 showed the dilatation to be progressing At no time has she shown any postoperative reflux See figures 4 and 5

Case 5 P P , a 3 year old girl, was admitted to the State University of Iowa Hospitals with a history of repeated episodes of chills, fever and pyuria since birth Physical examination, including neurological examination, was negative Excretory urograms demonstrated good function bilaterally and complete reduplication of both upper urinary tracts No function could be seen in the upper segment of the left kidney Cystography revealed complete ureteral reflux into all four ureters and renal pelves The reflux was most marked in the upper segments On cystoscopic examination no ureteral orifices could be seen, but a large saccule was present at each lateral boundary of the trigone On November 1, 1951, a vesicoureteral plasty was done on each ureterovesical junction

When the bladder was opened, two saccules large enough to admit the distal phalanx of the little finger were found at each lateral boundary of the trigone The lower ureter on each side was found in the depth of each saccule The upper ureter bilaterally opened into the roof of its respective saccule On each side, the intramural ureters were dissected free of the bladder wall and a short segment of both ureters drawn into the bladder The bladder wall was closed carefully under these newly created intravesical ureters

Postoperatively, the patient did well and when checked 3½ months later, there was no ureteral reflux by cystography The excretory urograms were improved when compared with the preoperative films Clinically, the patient has had no chills or fever since her operation

She has been carefully checked since her operation and never has demonstrated reflux into any of her four ureters The pyelograms have improved progressively and except for the upper segment on her left (which has never shown function) the pyelograms are normal Clinically, she has been greatly improved but does have occasional urinary tract infection which requires treatment Her last check-up examination was March 1955, three and one half years postoperatively See figures 6 and 7

Case 6 M M , a 3 year old girl, was admitted to the State University of Iowa Hospitals because of severe attacks of chills and fever which had occurred on an average of every 2 weeks for the preceding 6 months Associated marked pyuria and bilateral flank pain had been noted Physical examination was negative and there was no neurologic lesion demonstrable Excretory urograms revealed excellent function bilaterally, and mild bilateral calyectasis, hydroureter and complete re duplication of the left ureter and pelvis Cystograms revealed complete bilateral ureteral reflux On September 21, 1951, a right vesicoureteral plasty was performed

This patient has been carefully followed for 3½ years The reflux has been effectively stopped although a slight tendency to reflux still persists Her excretory urograms are normal and have shown a definite improvement over the pre operative ones Clinically, she is symptom free See figure 8

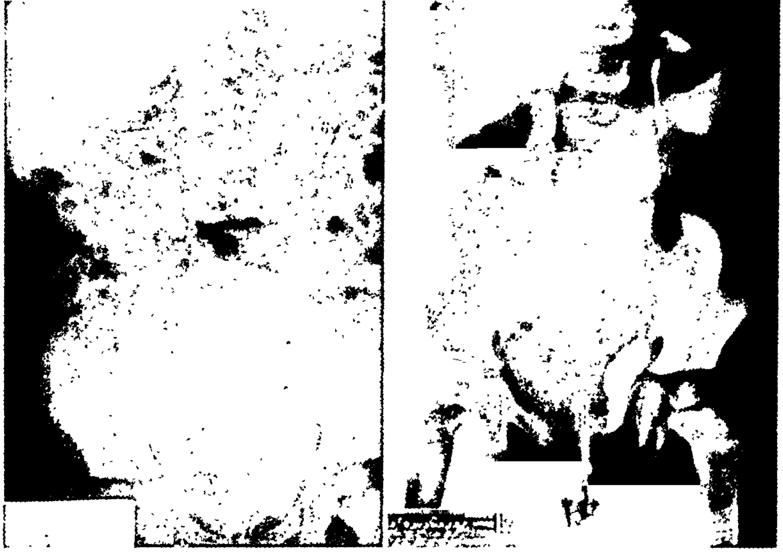

FIG. 6. Case 5. *A*, preoperative excretory urogram. *B*, preoperative cystogram. Complete cystogram reveals reflux into all 4 ureters and renal segments.

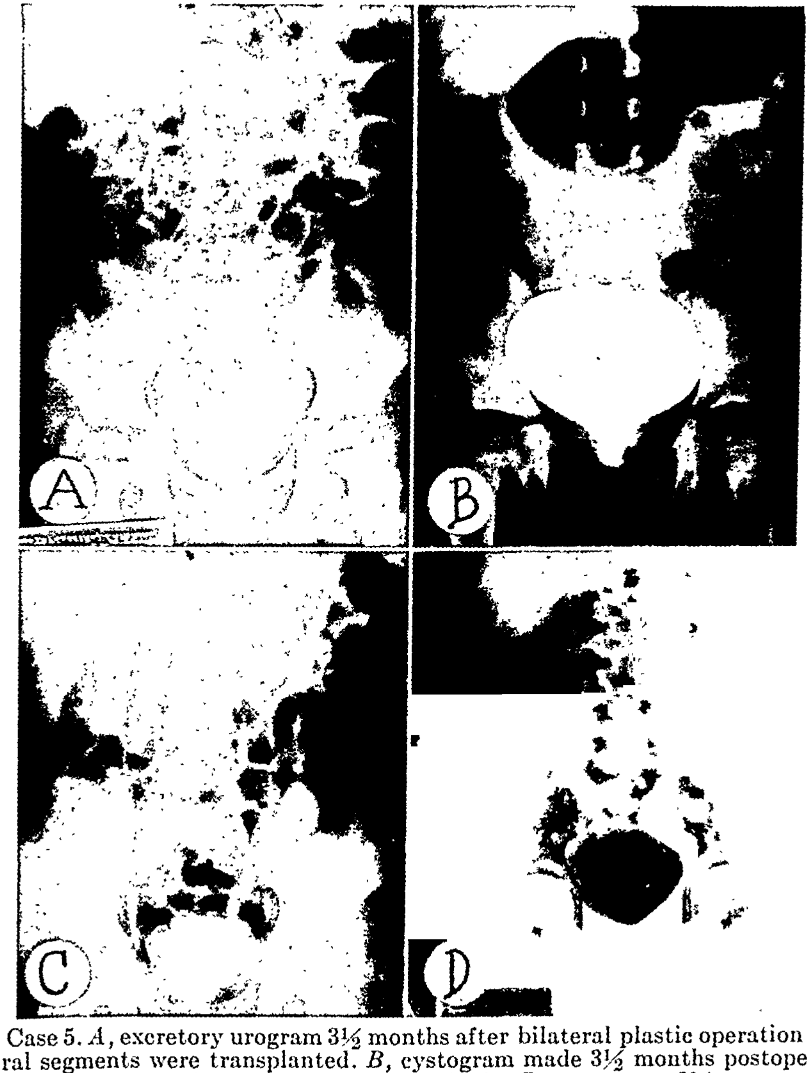

FIG. 7. Case 5. *A*, excretory urogram 3½ months after bilateral plastic operation in which all ureteral segments were transplanted. *B*, cystogram made 3½ months postoperatively. *C*, excretory urogram made 3½ years postoperatively. *D*, cystogram 3½ years postoperatively.

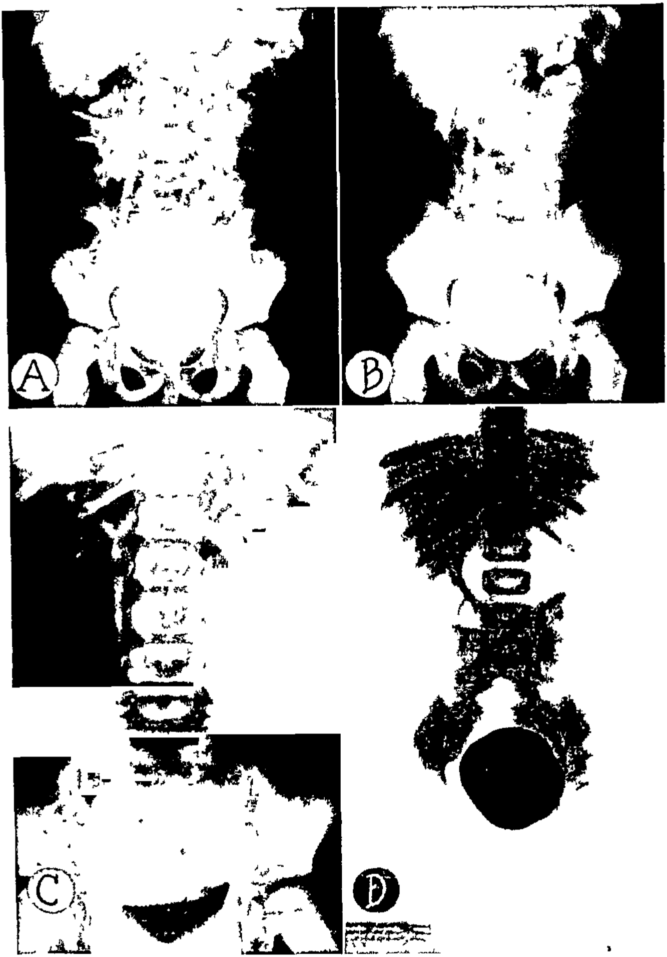

FIG 8 Case 6 *A*, preoperative excretory urogram *B*, preoperative cystogram *C*, postoperative excretory urogram. *D*, postoperative cystogram Note that reflux has stopped on both sides in spite of fact that operation was done only on right side Subsequent examinations have shown occasional reflux bilaterally

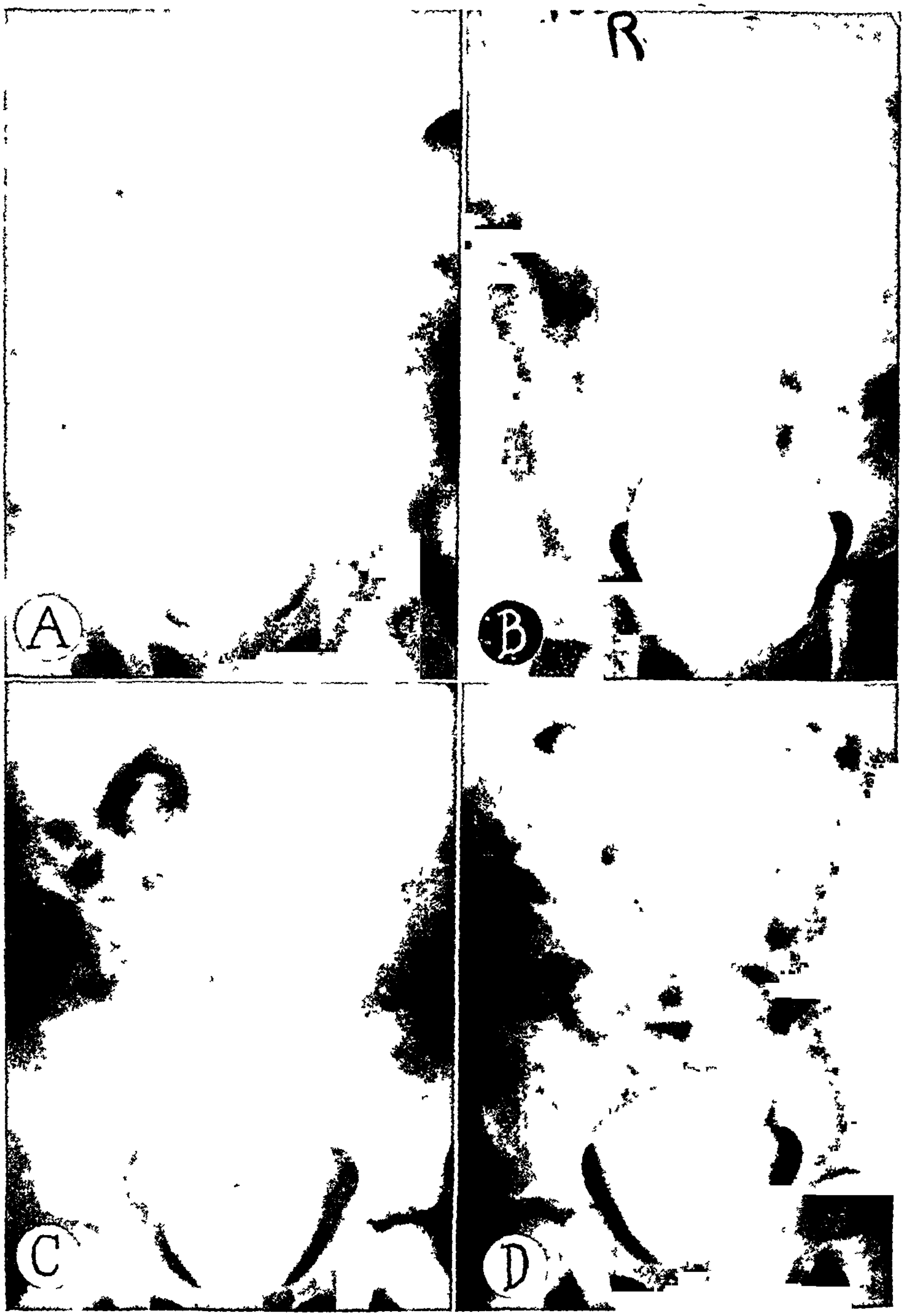

Fig. 9. Case 7. *A*, preoperative excretory urogram. Right kidney nonfunctioning throughout entire examination. *B*, preoperative cystogram. *C*, excretory urogram 2 years postoperatively. *D*, cystogram 2 years postoperatively.

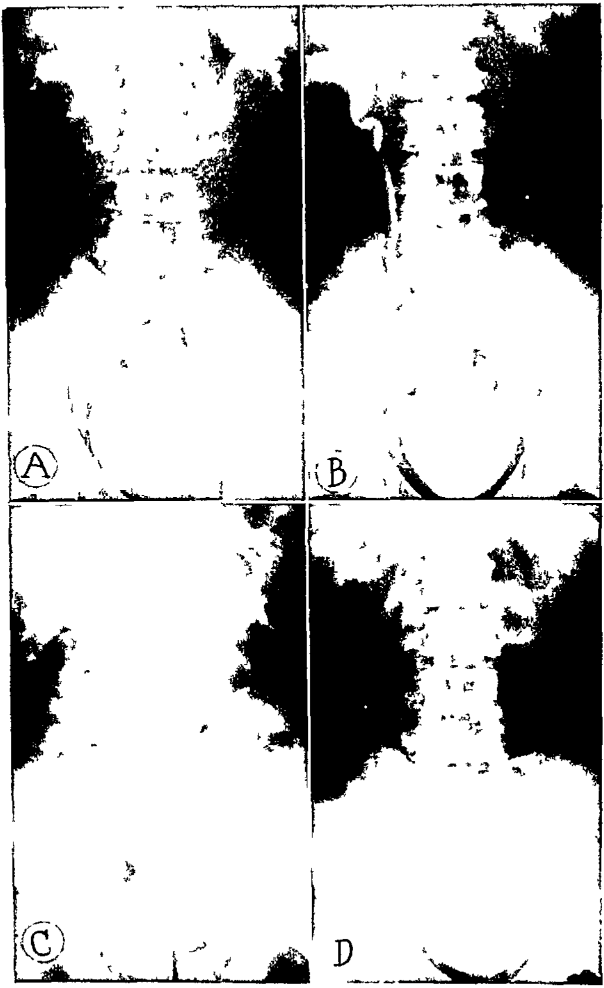

FIG 10 Case 8 *A*, preoperative excretory urogram *B*, preoperative cystogram Note saccule at right ureterovesical junction *C*, postoperative excretory urogram *D*, postoperative cystogram

Case 7. D. K., a girl aged 2, began to have recurring episodes of chills and fever and pyuria at age of 5 months. Her physical examination was negative including the neurologic examination. In February 1952, when the patient was 1 year old, a cystogram revealed right ureteral reflux and a bladder neck resection was done. The patient did not do well and a second bladder neck resection was done. The patient continued to have pus in her urine and chills and fever when she was taken off gantrisin. Pain developed also in the right upper abdomen. Physical examination was essentially normal. Delayed cystograms revealed bilateral ureteral reflux. Intravenous pyelograms revealed a nonfunctioning right kidney and a dilated, tortuous left ureter. The urine was chemically negative and microscopically showed numerous pus cells. On February 5, 1953, a bilateral ureterovesical plasty was done. The postoperative course was good. The pyuria and pain in the right flank disappeared and the episodes of chills and fever ceased. Several delayed cystograms done postoperatively have failed to reveal any recurrence of the reflux. The patient has also had several excretory urograms which revealed prompt bilateral function, a normal left kidney and marked improvement in the right kidney. See figure 9.

Case 8. A 19-year-old white man was seen on the urologic service at Park's Air Force Base, California because of pyuria and pain in the right flank. The pain had been present off and on for several years; no satisfactory diagnosis had been made. Excretory urograms revealed prompt bilateral function, both kidneys appearing essentially normal except for some dilatation in the lower portion of the right ureter. A cystogram revealed right vesicoureteral reflux and a large saccule or diverticulum on the right side of the bladder wall at the point where the ureter entered the bladder. Cystoscopic examination revealed that the right ureteral orifice was situated in the depth of a large diverticulum. In September 1954 a right vesicoureteral plasty was done.

The postoperative course was good. Following the operation the pain in the right flank has completely disappeared and the urine has remained consistently free of pus. Excretory urograms are essentially normal and the dilatation present in the lower portion of the right ureter has disappeared. Delayed cystograms fail to reveal any evidence of reflux. See figure 10.

DISCUSSION

It is our belief that the ability of the normal urinary tract to resist vesicoureteral reflux rests in the ureterovesical junction and is a co-ordinated and cooperative effort of the intravesical ureter and the muscles of the bladder wall through which it passes. Two distinct types of action occur at the ureterovesical junction which are designed to prevent the regurgitation of bladder contents up the ureter. The first of these is a primary function of the bladder muscle which lies underneath and supports the intravesical ureter. As the bladder fills and the intravesical pressure increases these muscles stretch and carry the intravesical ureter into a more oblique position as it passes through the bladder wall. The roof of the intravesical ureter is then compressed against its floor between the pressure of the bladder contents and the firm bladder muscles behind it. Thus the relationship between the bladder wall and the intravesical ureter is constantly changing as the bladder fills and empties While this activity is basically a function of the detrusor fibers underneath the ureter it is dependent upon the collapsibility of the intravesical ureter for its success in the prevention of reflux

The second of these activities of the ureterovesical junction designed to prevent reflux is a primary function of the intravesical ureter Immediately following the spurt of urine through the ureteral orifice the intravesical ureter and the lateral border of the trigone are pulled sharply upward carrying the ureteral orifice with it This must be the result of contraction of the longitudinal fibers of the intravesical ureter The lumen of the *intravesical ureter is actively occluded* by the contraction of its walls Also it is possible that this activity bends or angulates the intravesical ureter over the edge of the bladder muscles upon which it lies This defense against reflux is a valuable one as it occurs at a time when the ureter is very vulnerable to reflux, viz , immediately after the ureter has emptied its contents into the bladder

For the sake of completeness a third possible defense against reflux must be discussed This is theoretical and based on the assumption that Wesson and Young and Wesson[3] are correct when they suggest that contraction of the trigone helps to open the internal urinary sphincter during micturition When one considers that the fibers of the trigone sweep over the posterior lip of the bladder neck to insert around the verumontanum it becomes apparent that the trigone is admirably placed anatomically to do just that During voiding the intravesical *pressure rises rapidly to as high as 150 cm of water The susceptibility to reflux* is great at this time However, if the trigone is contracting at this moment the ureters would be pulled downward since they are continuous with the lateral borders of the trigone and the length of the intravesical segment of the ureters would be increased That such an increase in the length of the intravesical segment of the ureter could serve as a defense against reflux is supported by Gruber [4] He found that in species which are very susceptible to reflux (rabbits, cats and dogs) the trigone was poorly developed and the intravesical ureter was short, where as in humans and other species where reflux is rare, the trigone is well developed and the intravesical ureter is long

Based on the foregoing ideas we have come to think of our defenses against reflux as a dynamic relationship between the bladder wall on one hand and the intravesical ureter and trigone on the other hand It is a constantly changing fluid type of relationship which automatically adjusts to meet varying conditions within the bladder and ureter Any disease which destroys this relationship or alters the adaptability of one or both of the structures involved may result in vesicoureteral reflux Diseases which cause bladder trabeculation are frequently complicated by reflux These would include spastic neurogenic bladders secondary to cord injury or disease and diseases which cause urinary obstruction at or below the bladder neck Here the changes at the ureterovesical junction can be clearly visualized cystoscopically or by cystogram In certain other conditions

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✓[2] Wesson, M B Anatomical, embryological and physiological studies on trigone and of neck of bladder J Urol , 4 279–307, 1920

✓[3] Young, H H and Wesson, M B Anatomy and surgery of trigone Arch Surg , 3 1 37, 1921

[4] Gruber, C M J Urol , 21 567, 1929

in which the bladder wall becomes very thin there is insufficient muscle behind the ureter to support it in an intravesical position. This is probably the explanation of the reflux in the meningomyelocele cases. In certain other cases the explanation for the reflux must lie in the faulty development of the ureteral bud. It is noted that three of our cases had complete ureteral reduplication, one bilateral.

No discussion of reflux is complete without some mention of the part it plays in the dilatation of the upper urinary tract. It is recognized that reflux is often present in cases which have functional obstruction at the ureterovesical junction. The additional work load placed on the ureter by the reflux could account for the dilatation of the ureter but often the dilated ureter exists alone and no reflux can be demonstrated to account for it. In addition to preventing reflux the intravesical ureter must also allow ureteral urine to pass through it unobstructed. Perhaps these changes discussed above which destroy the capacity of the ureterovesical junction to resist reflux also cause it to fail in this second function and may result in a functional obstruction as well as in reflux. There is some clinical evidence to support this idea.[5] The relationship between vesicoureteral reflux and nonobstructive dilatation of the upper urinary tract is a close one and it may be that the ureterovesical junction is the key to both problems.

SUMMARY AND CONCLUSION

After observing the clinical and radiological course of these patients for almost four years we feel justified in making some conclusions. First, the operation effectively stops reflux. All patients included in this study had persistent, severe reflux preoperatively. Postoperatively, they were subjected to the most rigid testing we could devise, namely, the delayed cystogram consisting of 3 to 4 films over a period of one to two hours. Most of these patients have had two to three such examinations each year since their surgery. In spite of this only two of the fourteen ureters involved have shown any tendency to reflux.

Clinically, the improvement has been equally gratifying. Without exception each patient has either been cured of symptoms or has experienced a reduction in the frequency or severity of symptoms.

Of maximal importance in the evaluation of any procedure designed to correct reflux is its effect upon the upper urinary tract as judged pyelographically. In five of the eight cases the pyelogram has been improved and is today normal or nearly normal. In two cases pyelographic improvement was noted for two and a half years postoperatively but further dilatation has been occurring in the last year and a half. One kidney was damaged by the operative procedure and required nephrostomy drainage two and one half years postoperatively. All of the poor results were in the meningomyelocele group.

Our overall experience with this procedure has been quite gratifying and we believe it will earn a place in the treatment of reflux.

2100 Monument Blvd., Pleasant Hill, Calif. (J.A.H.)

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URETHRECTOMY SUBSEQUENT TO TOTAL CYSTECTOMY FOR PAPILLARY CARCINOMA OF THE BLADDER

CASE REPORTS

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It has been considered good urologic practice for many years to remove the ureter as well as the kidney when papillary carcinoma of the renal pelvis is found. This of course is done in an attempt to prevent seeding of the neoplasm down the ureter. The mucosa of the bladder and proximal urethra is similar in all respects to that of the renal pelvis and ureter, and is exposed to the same carcinogenic substances. Papillary tumors arising anywhere in this urothelium are identical histologically and are notorious seeders. It seems logical to us, therefore, to consider the urethra as bearing the same relation to the bladder as the ureter does to the kidney, in so far as papillary tumors are concerned. Following this line of thought, one would expect to find the urethra involved in an appreciable percentage of papillary bladder neoplasms, just as the ureter and bladder itself are often inoculated by seeding from a similar tumor of the renal pelvis. A survey of the literature at the present time, however, does not bear out this conclusion. Kiefer does warn that there seems to be an increase in the tendency for seeding to occur in the urethra following transurethral treatment of bladder tumors, and Campbell states that removal of the bladder and urethra may be required when there is widespread involvement of the bladder and urethra with papillary growths. But while many reports in the literature testify to the delayed appearance of papillary cancer in the bladder following nephrectomy and ureterectomy for renal neoplasm, there were no cases found in which similar tumors were reported as appearing in the urethra in the weeks or months following cystectomy for bladder carcinoma.

It has been our misfortune to observe this complication on two occasions. We wish to report these 2 cases and to offer our thoughts and suggestions as to the prevention of this serious sequela in the future.

CASE REPORTS

Case 1. L. L., a white man, 59 years old when first seen by us in October 1952, had undergone cystoscopy in February 1952 because of urinary retention. Multiple papillary tumors of low grade malignancy were found in the bladder dome and subtotal cystectomy had been performed. Rapid recurrences were noted in spite of repeated transurethral fulgurations, and were not even slowed down by the instillation of podophyllin on one occasion.

Our examination in October 1952 found him to be in good general and urological condition except for his bladder. Cystoscopic study showed this to be the site of many papillary growths, located in the dome, on the right lateral wall

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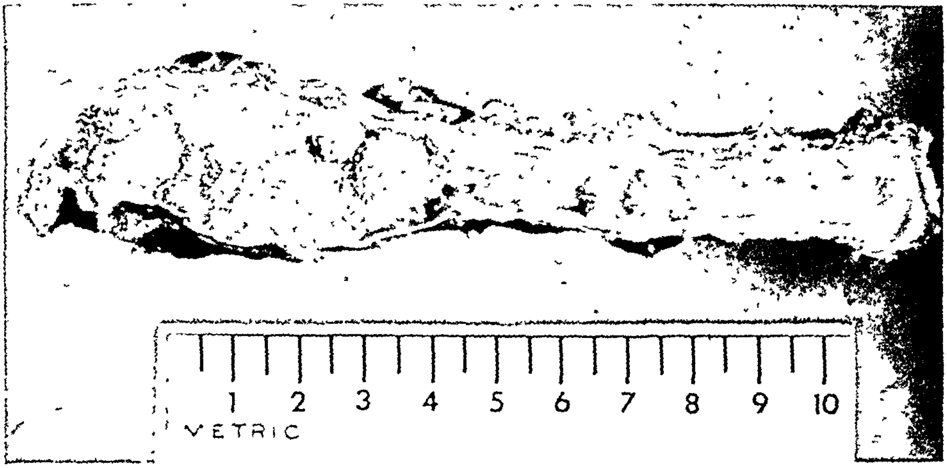

FIG. 1. Case 1. Urethra showing implants along its entire length

and at the bladder neck on the patient's left. No implants were evident on careful inspection of the prostatic and penile urethra.

Total cystectomy therefore seemed to offer this man his best chance of cure. Accordingly, on November 7, 1952 the bladder, prostate, and seminal vesicles were removed *en masse* and the ureters were transplanted into the sigmoid. Pathological study showed the bladder mucosa to be studded with small papillary areas of transitional cell carcinoma. These were mostly in situ changes with only a rare extension into the submucosa. At the left of the bladder neck, however, there was a larger mass of the same tumor structure which infiltrated the submucosa and muscularis of the bladder wall and also the prostatic tissue for a short distance.

The patient felt well during the months following his operation, but from time to time, he noticed that there was a little bloody discharge from his penis. Urethroscopic examination in September 1953 revealed the presence of many small papillary tumors. A biopsy was taken (reported as the same papillary transitional-cell carcinoma of low grade malignancy) and the whole mucosal lining was coagulated. At urethroscopy in March 1954 several areas of recurrent tumor were found and thoroughly fulgurated. Urethrectomy was advised, but the patient would not consent to it. When tumors were again found in July 1954, however, permission was given and the operation was performed (fig. 1).

Pathological study showed that many small masses of papillary transitional cell carcinoma (of medium grade malignancy) were scattered throughout the urethra. These changes were limited to the mucosa except in one area where infiltration of the muscular coat had occurred.

This patient lives in New Mexico and has not been seen recently. He wrote in December 1954 that he had a swelling or growth in his left groin. In all probability, this is metastatic carcinoma.

Case 2. E. S., a white 68-year-old man, was admitted to Parkland Memorial Hospital on June 16, 1954 with a history of frequent, burning urination accompanied by constant hematuria for the past 4½ years. Cystoscopy showed the

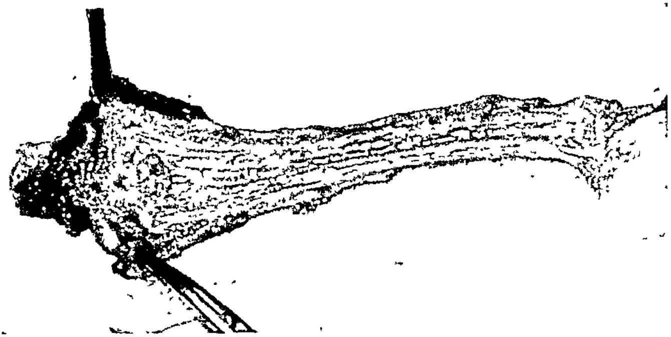

FIG. 2. Case 2. Urethra showing implant in bulbous portion

bladder to be diffusely involved with multiple, beefy, papillary tumors interspaced with areas of hemorrhage.

On June 28, 1954, the ureters were transplanted to the sigmoid and 3 weeks later, total cystectomy was done. Pathological study showed that many areas of papillary carcinoma were present with some invasion of the bladder musculature.

On November 3, 1954 (three and one-half months later) the patient was readmitted because of pain in the left hip. In the course of his examination, a little bloody discharge was noted at the urethral meatus and panendoscopy revealed that several small, papillary tumors were present in the bulbous urethra. These were biopsied and found to be identical in structure with the previously removed bladder carcinoma. Since x-ray examination showed no definite pathological process in the hip, attention was centered on the urethra and it was removed on November 24, 1954 (fig. 2). No invasion by the papillary lesions was found on pathological study.

In the following weeks, the patient complained of increasing pain in the left hip and on December 29, 1954, the left iliac crest was exposed surgically and was shown to be the seat of a large metastatic tumor of the same papillary type previously demonstrated in the bladder and urethra. X-ray therapy was administered over the crest and temporary improvement permitted the patient to be discharged on January 12, 1955.

We believe that each of these patients would have been spared much discomfort, mental anguish and expense if the urethra had been removed at the time of cystectomy. In addition, the chances of cure probably would have been increased.

DESCRIPTION OF OPERATION

In the preceding case reports urethrectomy was performed in the following manner: A median ventral incision was made in the skin of the penis extending from the external urinary meatus to the proximal extent of the bulbous urethra,

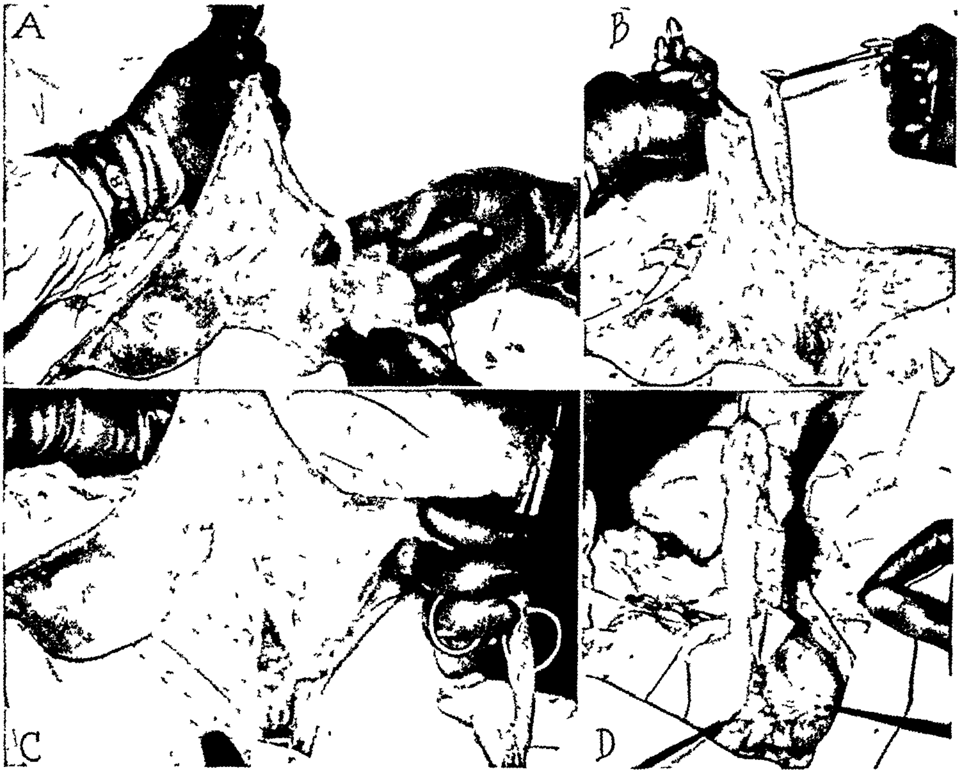

FIG. 3

bivalving the scrotum and exposing the entire corpus spongiosum. This corpus was then carefully dissected free from the corpora cavernosa beginning in the midportion (fig. 3, *A*) and extending in each direction until it was attached only at the external urinary meatus and at the urogenital diaphragm. The corpus spongiosum was then clamped and cut just proximal to the fossa navicularis leaving the glans intact (fig. 3, *B*). The bulbous urethra and the remainder of the membranous urethra were then dissected free at the site of the urogenital diaphragm (the prostatic urethra and a portion of the membranous urethra having been removed at the time of the previous cystectomy) (fig. 3, *C*). A meatotomy was done laying open the fossa navicularis for complete inspection. The corpora cavernosa were approximated with 000 chromic interrupted sutures placed in Buck's fascia, and the two halves of the divided scrotum were approximated with interrupted sutures of the same material. A Penrose drain was left in the depth of the wound exiting at the penoscrotal junction. The skin was approximated with a subcuticular suture of fine plain catgut (fig. 3, *D*).

DISCUSSION

We have stated in our preliminary remarks that we believe that the urethra and bladder bear the same relationship to each other as the ureter and kidney pelvis insofar as papillary tumors are concerned. We suggest that the absence of reports of the appearance of urethral implants weeks or months after cystectomy for bladder tumor may be explained on the basis that early followup urethroscopic studies were not done All reports covering series of total cystectomies for bladder tumor show a large percentage of metastatic recurrences It is easy to postulate that perhaps the metastatic growths from papillary tumors had their origin in implants in the urethra which was left in situ It is possible that early *urethroscopic followup might have revealed* the presence of these lesions before more distant overshadowing metastases occurred

It is not within the scope of this paper to attempt to point out the indications for total cystectomy, but we believe that when this procedure is done in an effort to eradicate papillary carcinoma of the bladder, urethrectomy should also be considered if one is to avoid an occasional unfortunate occurrence such as we have reported However, if the urethra is left in situ, neoplastic seeding of its *mucosa might be detected in its incipient stage by early and frequent urethroscopy* If such metastases do occur, urethrectomy without further delay might still be in time to effect a cure After the bladder and prostate are gone, the urethra serves no function whatsoever, and with its removal the patient loses a liability and not an asset

SUMMARY AND CONCLUSIONS

Two cases are reported in which implants appeared in the urethra months after cystectomy was done in an effort to cure papillary carcinoma of the bladder

The suggestion is made that this may occur more frequently than one would expect from the lack of similar reports in the literature

It is also suggested that these implants might be the origin of distant overshadowing metastases

If cystectomy is decided upon, it is believed that a better chance for cure might be obtained if the urethra were *removed along with the bladder*

If urethrectomy is not done, early and frequent urethroscopic examination is advocated

Thus, incipient implants may be discovered and adequate measures taken

We propose that such "adequate measures" should include at least a consideration of secondary urethrectomy

Operative steps for such a procedure in the male are given This might be an independent operation (as in our cases) or it could be combined with a perineal freeing up of the prostate and seminal vesicles at the beginning of total cystectomy In the female, it is, of course, a very simple matter to remove the urethra along with the bladder

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CARCINOMA OF THE PENIS IN A MAN CIRCUMCISED IN INFANCY

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Carcinoma of the penis occurring in a Jew ritually circumcised during infancy is a rare event. In 1953 Marshall[1] found in the literature 2 reports of penile carcinoma in circumcised Jews and presented one additional case. The case described below is a fourth.

CASE REPORT

J. F. (N.Y.H. No. 701 562) was a 49-year-old Hebrew who had undergone ritual circumcision in Europe. He complained of a painless sore which had begun 3 years previously as a red pimple on the left side of his penis. This lesion grew very slowly and produced a grey scale which would accumulate on its surface only to be lost during intercourse. Following these abrasive episodes a few drops of blood would appear and then cease. The patient denied any history of venereal disease or trauma. He had not married until he was 40 years of age which is of interest inasmuch as Marshall's patient was a 73-year-old bachelor. The patient had no genitourinary complaints and his general condition was otherwise excellent.

The lesion was found 1 cm. below the coronal sulcus in the region previously occupied by the base of the prepuce. It was ovoid in shape, 5 mm. in its greatest length and 3 mm. to 4 mm. wide. The surface was hard, without discharge and covered with a grey heaped-up scale. The entire lesion was freely movable and unattached to the underlying fascia. Squeezing the lesion did not produce pain. There were no enlarged inguinal nodes.

The entire lesion was excised elliptically with a good margin. Microscopically the stratified squamous epithelium was thickened and the normal cell layers lost. The cells were disorganized and pleomorphic with numerous mitoses. There were also many vacuolated "target cells" with centrally placed nuclei. Although, as just described, much of this lesion appeared to be a carcinoma in situ (fig. 1) there were regions consisting of definitely invasive epidermoid carcinoma in which keratinizing islands of tumor cells lay in the corium beneath the more normal epithelium (fig. 2).

COMMENT

It is difficult to prove beyond question that this individual was circumcised as an infant. We have, however, not only his word but that of his family, one member of which is a physician with whom we are associated. There is no patent reason for doubting the veracity of the statements made by either the patient or his family.

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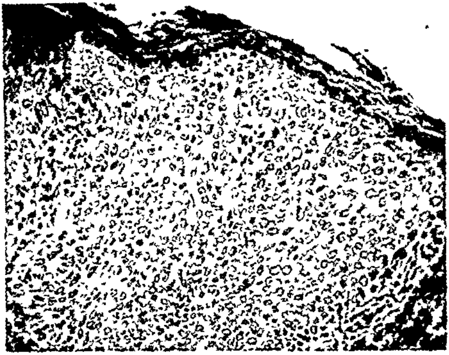

FIG. 1. Area of carcinoma in situ, in which normal stratification of epithelial cells has largely disappeared and in which there are many mitotic figures and many hyperchromatic abnormal nuclei. Some of latter, typically, are situated in vacuoles.

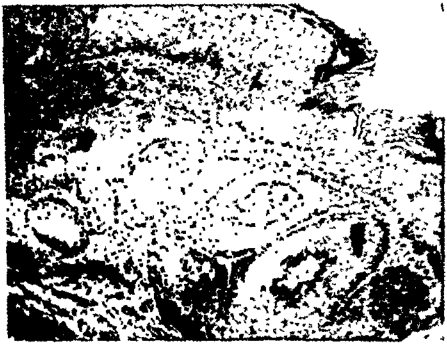

FIG. 2 Invasion of epidermoid carcinoma into corium beneath normal epidermis at margin of carcinoma in situ.

CONCLUSION

An epidermoid carcinoma of the penis developed in a Jewish man who had been ritualistically and adequately circumcised during infancy. This is the fourth case to be reported.

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BILATERAL INTERSTITIAL CELL TUMOR OF THE TESTICLE: REPORT OF ONE CASE OBSERVED FOURTEEN YEARS

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Bilateral interstitial cell tumors of the testicle are very rare. The world literature to date reports only three cases: Kaufmann,[1] Garvey and Daniel,[2] Flynn and Serverance.[3] In this paper we wish to present the fourth. The case herein reported has been previously mentioned (including photograph) in a review by Melicow, Robinson, Ivers, and Rainsford.[4] However, at the time of their report full clinical development of the case had not transpired. The case being presented in this paper has been followed approximately fourteen years; and here its clinical and histological manifestation in this period of time shall be described as it developed.

CASE REPORT

W. G. was first seen in October 29, 1940 in Jackson Memorial Hospital, Miami, Florida because of an acute onset of chills and fever. Past history at the time of this admission revealed the following developments. He was born on February 10, 1934, the fourth child of a normal full term delivery who was breast fed and at birth weighed 8 pounds. His growth and development were normal until the age of three at which time his mother noted abnormal growth of genitalia, pubic hair, and accentuation of male characteristics. Voice changed at age of five. At age of six he had mentality of the second grade with low average marks. He was always active, strong, and alert as a youth. Physical examination on the first hospital admission revealed a stature of a thirteen or fourteen-year-old boy whose facial characteristics were those of an adolescent male. The voice sounded like an adult's. The genitalia were the size of an adult with pubic hair. Treatment on the first admission was for tularemia with symptoms subsiding and patient was discharged on November 4, 1940. On September 22, 1943, he was seen by the late Dr. John E. Hall of Miami because of an enlarged left testicle that felt heavy and was painful on manipulation. Physical examination revealed a stature of a youth of eighteen or nineteen years of age. The chest, abdomen, and foreparts of the thighs were covered by dark hair. The left testicle was enlarged ten times the normal size, felt heavy and did not transilluminate. The cord could not be isolated by pressure. Tumor mass filled the whole left side of the scrotum causing the skin to be tense and glisten but not adherent. The right testicle was markedly enlarged for his age though not as large as the left. X-rays

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[1] Kaufmann, E.: Ueber Zwischenzellengeschwulete des Hodens. Verhandl. d. deutsch path. Gesellsch., **11:** 237, 1907.

[2] Garvey, F. K. and Daniel, T. B.: Bilateral interstitial cell tumors of the testicle. J. Urol., **66:** 713, 1951.

[3] Flynn, P. T. and Severance, A. O.: Bilateral interstitial-cell tumors of the testes. Cancer, **4:** 817, 1951.

[4] Melicow, M. M., Robinson, J. N., Ivers, W. and Rainsford, L. K.: J. Urol., **62:** 672, 1949.

of the skeletal system revealed the development of an average individual of 18 years of age The epiphyseal lines of the hand and feet were already closed, those of the wrist, shoulder, and knees were just barely discernible All of the bones were heavily calcified and of strong, well-built character The sella turcica was on the small side of normal and showed no erosion or other abnormal signs No intracranial calcification was observed Laboratory results showed a hemoglobin of 91 per cent, white blood cell count of 8,500, the nonprotein nitrogen was 31 1 mg per cent, platelets were 292,500, and the basal metabolic rate was plus 17 On September 25, 1943 a left orchiectomy was performed by Dr Hall at Riverside Hospital, Miami, Florida At operation the tumor was found to involve the entire testicle including the globus major and minor

Pathology report Grossly the left testicle weighed about 130 gm The tunica albuginea was present throughout There was bulging in some areas, no tumor infiltration or perforation was noted Cross section revealed a uniform, greyish-brown tissue giving the aspect of smoked fish meat with islands which were darker than the brown greyish matter The epididymis gave the same picture

Microscopic and histological appearance revealed the capsule was intact The testicular pattern was replaced by a tumor consisting of irregular shaped cells with smaller and larger nuclei and a fine chromatin network The cytoplasm did not accept eosin readily, most probably due to an accumulation of lipoid substances and fine pigment dust No crystals were present These cells were arranged in groups separated from each other by strands of connective tissue Sometimes one has the impression as though the tumor tissue offers cellular arrangements usually seen in liver or adrenals No testicular tubules were present Diagnosis Interstitial cell tumor (diffuse type) See figure 1

Postoperative course was uneventful Following the operation no regression of precocious development was noted and examination of the right testicle made it suspicious that the latter was involved by a tumor of perhaps a similar type Permission was asked for biopsy, but the request was denied From this time the patient lived a normal life and enjoyed good health until 1951 when an eye infection developed and he appeared to be losing complete vision of the left eye He was admitted for treatment on September 17, 1951 to Jackson Memorial Hospital Physical examination revealed blood pressure 130/85 in a well developed male of short and stocky build The right testicle was three times the normal size, hard and nodular Ejaculate specimen revealed no sperm Laboratory procedures performed at this time revealed a hemoglobin of 92 per cent, the white blood count was 10,660, the nonprotein nitrogen was 37 mg per cent, the phosphorus was 3 8 mg per cent The urine showed a few white blood cells The urine culture produced E coli and A aerogenes Basal metabolic rate was plus 36 and 41 Kahn was negative Excretory urography was normal Friedman test was negative The excretion of 17-ketosteroids was 81 mg /24 hrs During this hospitalization, permission was obtained for biopsy which was performed on September 19, 1951

Pathology report Microscopic examination of tissue revealed a tumor com-

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BILATERAL INTERSTITIAL CELL TUMOR OF THE TESTICLE: REPORT OF ONE CASE OBSERVED FOURTEEN YEARS

PHILIPP REZEK AND H. C. HARDIN, JR.

From the Departments of Pathology and Urology of the Jackson Memorial Hospital, Miami, Fla.

Bilateral interstitial cell tumors of the testicle are very rare. The world literature to date reports only three cases: Kaufmann,[1] Garvey and Daniel,[2] Flynn and Serverance.[3] In this paper we wish to present the fourth. The case herein reported has been previously mentioned (including photograph) in a review by Melicow, Robinson, Ivers, and Rainsford.[4] However, at the time of their report full clinical development of the case had not transpired. The case being presented in this paper has been followed approximately fourteen years; and here its clinical and histological manifestation in this period of time shall be described as it developed.

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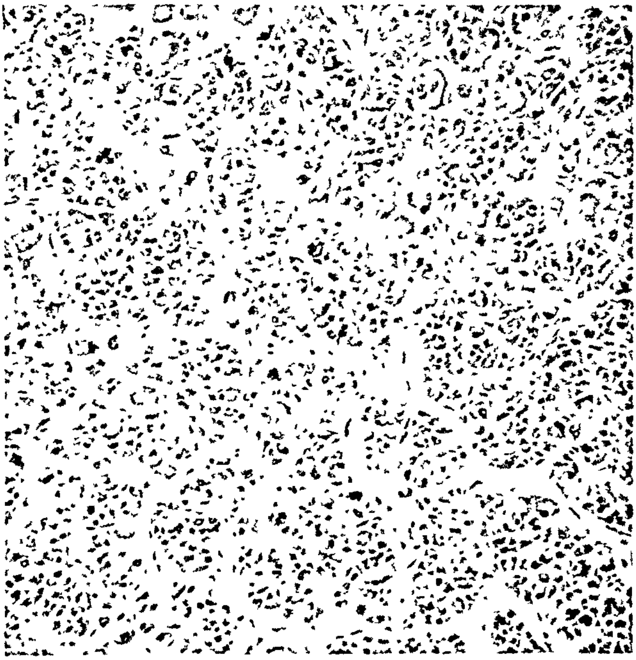

FIG. 1. Left testicle removed, 1943. Diffuse type interstitial cell tumor showing delicate frame work and no evidence of tubules present.

posed of closely packed cells. The vessels were not invaded but no testicular tissue was present. The single cells showed ovoid or polyhedral outlines, granular cytoplasm, and 1–2 eccentrically located nuclei. No mitoses were noted. The tumor was benign. Diagnosis: Typical interstitial cell tumor.

After discharge from the hospital the patient lived a normal life for about one and one-half years; then he began to complain of severe pain in the remaining testicle. With this presenting symptom and a fear of the tumor becoming malignant, the patient asked for the remaining testicle to be removed. During this period he had normal sexual desires, nocturnal emissions and practiced masturbation. No heterosexual experiences were practiced. Before surgery was performed a 17-ketosteroid determination was made; total 91 mg./24 hrs., alpha 36 mg. and beta 55 mg. On January 21, 1953 right orchiectomy was performed.

Pathology report (figs. 2, 3, 4): The gross specimen consisted of a right testicle which was markedly enlarged and much heavier than normal. It weighed about 160 gm. but retained a normal shape, measuring about 8 by 4 cm. in its largest diameters. The surface was smooth and glistened. No infiltration was noted and the vessels in the tunica were distended and slightly protruded. The capsule was pinkish-grey. A large part of the cord was present. The removed organ offered a peculiar consistency; it felt nodular, the nodules were rather firm in some areas, softer in others and it could already be felt that they were lodged into a rather firm rubbery mass. The latter was much less extensive in amount than the nodules. The cut surface showed the testicle occupied by brownish-black (chocolate brown) nodules that measured from one to two centimeters in diameter. Even within these nodules, however, there were areas of bright

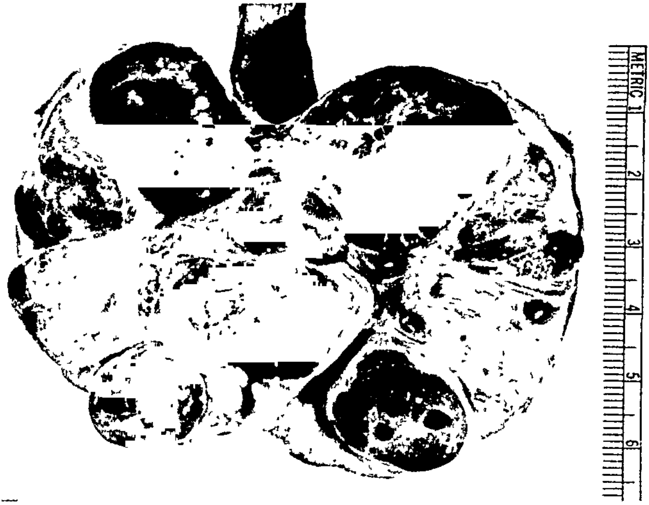

FIG. 2. Gross specimen of right testicle. Nodular type of interstitial cell tumor

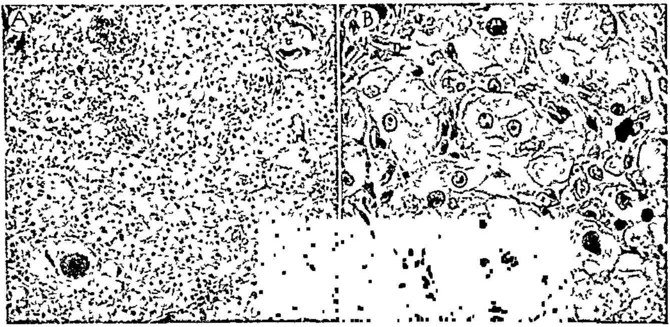

FIG. 3. *A*, right testicle. Typical interstitial cell tumor, nodular type. *B*, higher magnification.

brownish connective tissue. Between the nodules a greyish-white tissue was present which corresponded to the firmer part of the tumor described previously. Grossly, the capsule did not seem to be invaded.

Numbers of special stains were made, such as hematoxylin-eosin, trichrome, iron-hematoxylin and fat stains. The following description gives the picture drawn from all these different stains. Microscopic: The tumor consisted of closely packed, polyhedral cells with a central or eccentric small nucleus. There was no evidence of pleomorphism or polychromasia. The cellular cytoplasm, which

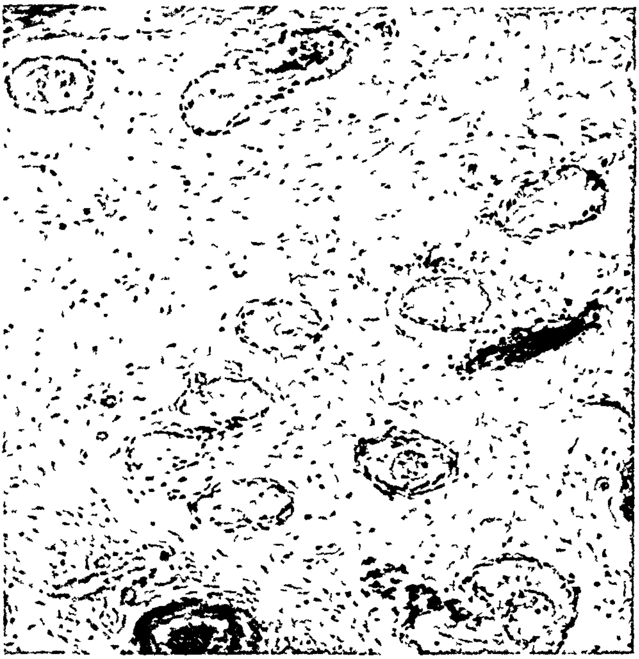

FIG. 4. Right testicle. Tubules atrophic with edema and fibrosis in internodular spaces

was very plentiful, was sometimes granular, sometimes homogeneous; no evidence of crystals was present. However, between the tumor nodules, there were strands of connective tissue and blood vessels, all of which were very well preserved. From time to time, one saw a giant cell of the foreign body type but no inflammatory reactions were seen. The cytoplasm of these giant cells was a dirty pink color, most probably due to the accumulation of lipoid substances and a fine pigment was also noticed. The pattern of the tumor resembled adrenal tissue. Sections that were taken from the connective tissue area between the large areas showed two different features. First of all, islands of typical interstitial cells which did not show the same pattern as the tumor but only a similarity inasmuch as the cells were much smaller and the islands were microscopic in size. Secondly, the connective tissue was occupied by blood vessels and by atrophic tubules which could be identified as such only the presence of a thickened, hyalinized basal membrane. In some instances, there was also an inflammatory reaction surrounding these tubules. This reaction consisted of only lymphocytes, plasma cells and large mononuclears. It was very possible that the small islands of interstitial cells described were the starting points of larger tumor plaques. The cord did not show any pathological process. There were no signs of malignancy. Diagnosis: Interstitial cell tumor, nodular type.

Postoperative course was uneventful. Since the operation patient noticed no change in libido, and there was growth of beard for six months. After this he observed a decrease in the number of times he needed to shave. The voice became lighter; there were no nocturnal emissions. The latter condition lasted approximately six months, after which there was a return of all normal activities. Since operation two 17-ketosteroid determinations were made: December 17, 1953, total 3 9 mg—alpha 3 9 mg and beta 0 mg , May 20, 1954, total 2 1 mg—alpha 2 1 mg and beta 0 mg

At the present patient is living a normal life on testosterone His hair lines, muscles, and voice are those of his age Examination of the prostate by rectal palpation revealed a normal prostate for this age

DISCUSSION

Interstitial cell tumors of the testes are generally used synonymously with Leydig cell tumors, gynandroblastomas, and interstitiomas This tumor exists in the form of diffuse sheets, cords, masses, or nests of cells with occasionally an alveolar arrangement In previous articles there has been much controversy whether some of the cases were true interstitial cell tumors or hyperplasia of interstitial cells Warren and Olshausen[5] give a good comparison between the two "In hyperplasia there is an increase of interstitial cells between the tubules beyond the limits of growth Whereas, in tumors there is a discrete nodule or group of interstitial cells locally replacing or displacing the seminiferous tubules " Attention is called in our case to the fact that the left testicle showed an homogeneous texture while the right testicle presented a characteristic nodular type So far this combination, to our knowledge, has not been mentioned in the literature

The etiologic factors concerned in the development of interstitial cell tumors of the testes are not known However, experimental production of this tumor has been performed by a few authors Bonser and Robson, 1940[6] reported on production of this tumor of the testes in strong A strain mice resulting from weekly subcutaneous injections of triphenylethylene in sesame oil Hooker and Pfeiffer, 1942[7] reported production of interstitial cell tumors in mice by injection of estradiol benzoate and stilbestrol Gardner and Boddart[8] developed interstitial cell tumors in hybrid C C mice, by weekly subcutaneous injections of 50 to 100 micrograms of tri-p anisyl chloroethylene (TACE) It appears that with excessive amounts of estrogens in certain mice this tumor can be produced Interstitial cell tumors occasionally occur spontaneously in horses and birds and are common in old dogs[9, 10] The fundamental chemical and physiological mechanism that brings about this condition remains to be explained

Clinical manifestations of this tumor vary In children, they include precocious puberty, i e , voice changes, adult distribution of hair, adult musculature development, mental maturity, and sexual activities of an adult including erections and ejaculation In adults, there are few or no endocrinological symp-

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[5] Warren, S and Olshausen, K W Interstitial cell growths in testes Am J Path , **19** 307, 1943

[6] Bonser, G M and Robson, J M Effects of prolonged oestrogen administration upon male mice of various strains development of testicular tumors in strong A strain J Path & Bact , **51** 9, 1940

[7] Hooker, C W and Pfeiffer, C O The morphology and development of testicular tumor in mice of the A strain receiving estrogens Cancer Research, **2** 759, 1942

[8] Gardner, W W and Boddard, J Testicular interstitial cell tumors in hybrid mice given tri p anisyl chloroethylene Arch Path , **50** 750, 1950

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[10] Ruddich, H B and Willis, R A J Path Bact , **55.** 165, 1943

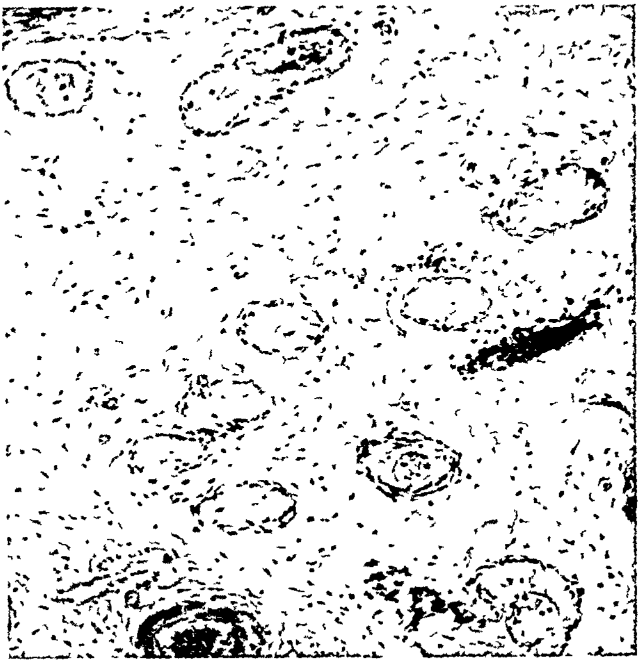

FIG. 4 Right testicle. Tubules atrophic with edema and fibrosis in internodular spaces

was very plentiful, was sometimes granular, sometimes homogeneous; no evidence of crystals was present. However, between the tumor nodules, there were strands of connective tissue and blood vessels, all of which were very well preserved. From time to time, one saw a giant cell of the foreign body type but no inflammatory reactions were seen. The cytoplasm of these giant cells was a dirty pink color, most probably due to the accumulation of lipoid substances and a fine pigment was also noticed. The pattern of the tumor resembled adrenal tissue. Sections that were taken from the connective tissue area between the large areas showed two different features. First of all, islands of typical interstitial cells which did not show the same pattern as the tumor but only a similarity inasmuch as the cells were much smaller and the islands were microscopic in size. Secondly, the connective tissue was occupied by blood vessels and by atrophic tubules which could be identified as such only the presence of a thickened, hyalinized basal membrane. In some instances, there was also an inflammatory reaction surrounding these tubules. This reaction consisted of only lymphocytes, plasma cells and large mononuclears. It was very possible that the small islands of interstitial cells described were the starting points of larger tumor plaques. The cord did not show any pathological process. There were no signs of malignancy. Diagnosis: Interstitial cell tumor, nodular type.

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However, in our case we show an interesting curve in the 17-ketosteroid determinations The initial test was taken after the first orchiectomy and was about nine times the normal, with the beta portion being greater than the alpha Then it was observed that following the removal of the second testicle the values dropped to normal or subnormal with the beta portion disappearing completely The disappearance of the beta portion may be explained on the basis that the source (the testicles) was removed Also there must be a factor in the testicle that stimulates the adrenals causing an elevation of the alpha portion, because after removal of the testicles, this portion became normal again Whether this is a typical curve remains to be seen

SUMMARY

A case of a bilateral interstitial cell tumor observed for fourteen years is reported The tumor was of the diffuse and nodular type respectively The clinical, biological, and morphological features of the case are discussed

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[17] Hunt, V C and Budd, J W Gynecomastia associated with interstitial cell tumor of the testicle J Urol , **42**. 1242, 1939

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TREATMENT OF ACUTE EPIDIDYMITIS WITH THE ANTIBACTERIAL DRUGS AND THE INTRAMUSCULAR INJECTION OF STREPTOKINASE

JOSEPH M. MILLER, JOHN A. SURMONTE, MILTON GINSBERG AND FRANK B. ABLONDI

From the Surgical Service, Veterans Administration Hospital, Fort Howard, Maryland and the Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

Patients with acute epididymitis are usually treated with rest in bed, elevation of the scrotum, application of ice to the involved area and administration of one of the antibacterial drugs. A review of the course of six unselected patients at this hospital showed that an average of about nine days was required for the disease to subside using this form of treatment.

Recently it has been demonstrated that the administration of an antibacterial drug and the intramuscular injection produced profound changes in the inflammatory barrier.[1] A reversal of inflammation and absorption of edema were effected.

Two methods of administration of streptokinase were used. In 4 patients in this series, 5,000 units of streptokinase were mixed with 0.5 cc of the plasma of the patient to provide a solution of plasmin outside the body of the patient. The mixture was injected intramuscularly immediately. Studies in patients with other types of infection showed that beneficial effects could be obtained by the use of streptokinase alone from plasmin made inside the body of the patient. This method was used on 1 patient in this series. Treatment with streptokinase was given twice daily for 3 days. Bed rest, elevation of the scrotum and the administration of one of the wide spectrum antibiotics were used. An average of about 4.8 days was required for the disease to subside.

Varidase, which contains streptokinase and streptodornase, was used as the source of streptokinase. The streptodornase in the mixture may be disregarded. The varidase is dissolved in physiologic saline so that the final concentration of streptokinase is 10,000 units per cubic centimeter. The solution was stored in the refrigerator when not being used. A fresh solution was made daily.

CASE REPORT

A 64-year-old white man was admitted to the hospital on December 3, 1953 with a painful swelling of the right epididymis of about two days' duration. The right epididymis was enlarged, irregular and tender. The patient was put to bed and the scrotum elevated. Ice was applied to the area. Streptomycin, 0.5 gm. and aqueous procaine penicillin G, 300,000 units were given intramuscularly twice daily from December 3 through December 9. Terramycin, 0.25 gm. was given orally 4 times a day from December 9 through December 14. By December

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[1] Miller, J. M., Surmonte, J. A., Ginsberg, M. and Ablondi, F. B. Clinical experience with the injection of streptokinase intramuscularly in the treatment of infection and edema. Maryland State M. J., 4: 188–193, 1955.

14, the pain and tenderness had disappeared but the epididymis was still slightly enlarged and irregular The patient was discharged from the hospital on December 17

The patient was admitted to the hospital on August 15, 1954 with severe pain in the left side of the scrotum due to left acute epididymitis of about four days' duration The temperature was 104F The left side of the scrotum was edematous and the left epididymis was enlarged to about three times normal size and tender The patient was kept in bed and the scrotum supported Terramycin, 0 25 gm was given orally four times daily from August 15 through August 22 The patient was given 5,000 units of streptokinase in 0 5 cc of physiologic saline intramuscularly twice daily from August 16 through August 19 for a total of 6 doses On August 17, the pain had lessened The edema of the scrotum had subsided moderately The epididymis was less tender and had decreased slightly in size On August 18, the pain had disappeared The edema of the scrotum had subsided Only slight tenderness remained in the epididymis which had decreased moderately in size On August 21, the patient was asymptomatic Slight induration was present in the epididymis He remained in the hospital for evaluation of his arteriosclerotic heart disease The patient was discharged from the hospital on September 1, 1954

COMMENT

Profound changes in the reversal of inflammation and the absorption of edema can be produced by the administration of an antibacterial drug and streptokinase. The presumed explanation of the phenomenon is that streptokinase activates plasminogen in the euglobulin fraction of the blood to plasmin Plasmin prevents the change of fibrinogen to fibrin and liquifies fibrin One of the localizing barriers of infection is apparently removed and a greater concentration of the antibacterial drugs at the involved area effected This results in more rapid cure of the patient

SUMMARY

The combination of an antibacterial drug and the administration of streptokinase intramuscularly reverses the inflammatory reaction and causes the absorption of edema Further investigation of the phenomenon is indicated

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A HISTOPATHOLOGIC SEARCH FOR CHRONIC SEMINAL VESICULITIS

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Chronic seminal vesiculitis is considered to be a common disease. In 1941 Hedin[1] contended that almost all infections involving the prostate gland also involved the seminal vesicles. Dillon and Blaisdell,[2] and Hyams, Kramer and McCarthy[3] carried out histopathologic studies which purport to show correlation of inflammatory disease in the prostate and the seminal vesicles. The incidence of chronic seminal vesiculitis in a large group of unselected postmortem examinations constitutes the basis of this study.

METHODS

The material consists of the lower urinary tract and genital organs of 161 men who came to routine autopsy. The age incidence was: 14.2 per cent, 21–40 years; 39.1 per cent, 41–60 years; 38.5 per cent, 61–80 years and 8.0 per cent over 81 years. The youngest patient was 21 and the oldest 97 years of age. Systemic disease processes among these patients include 8 cases of diabetes mellitus and 50 malignant neoplasms. There were 4 instances of leukemia and 4 malignant lymphomas. Subacute bacterial endocarditis was present in 9 patients.

In the dissections, the urinary bladder, prostate gland and the seminal vesicles were removed *en masse* and examined grossly. The bladder and prostate were incised longitudinally in the ventral surface and evidence of gross abnormality was noted. After fixation in 10 per cent neutralized formalin each prostate was sectioned transversely at the level of the verumontanum. Sections at this level adequately demonstrate the posterior urethra, the ejaculatory ducts and the prostatic ducts and acini.

The seminal vesicles were sectioned in the frontal plane, including the junction with vas deferens. The thickness of the walls was estimated and examination was made for evidence of obstruction of the seminal ducts.

Due to the large size of some of the specimens and the necessity of examining the entire sections, these blocks were bisected. Thus from the 161 specimens, 294 slides were prepared from the prostate glands and 207 from the seminal vesicles. The tissues then were stained with hematoxylin and eosin.

Read at annual meeting, American Urological Association, Los Angeles, Calif., May 16–19, 1955.

Note by editor. Doctor Calams' manuscript was awarded second prize in the 1955 prize essay competition sponsored annually by the American Urological Association under the Committee on Scientific Research, Dr. Miley B. Wesson, chairman.

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[3] Hyams, J. A., Kramer, S. E. and McCarthy, J. F.: The seminal vesicles and the ejaculatory ducts. Histopathologic study. Tr. Sect. Urol. A.M.A., pp. 100–116, 1931.

RESULTS

Of 50 cases which I examined grossly, the seminal vesicles were found in a loose stroma and were protected by their own fascias, the posterior bladder wall, the prostatic capsule and Denonvilliers' fascia. Only 2 instances of perivesicular induration with adhesions were found. This was associated with prostatovesicular abscess in one instance and with extension of prostatic carcinoma in the other. The fascial coverings of the vesicles stoutly resist penetration of inflammation from without. This was demonstrated in an instance of adjacent perirectal abscess with no evidence of inflammation of the seminal vesicles.

The majority of the seminal vesicles were composed of thick-walled convoluted tubules. However, 30.6 per cent of the vesicles were dilated and cystic in appearance (fig. 1). They measured up to 5.8 by 2.0 cm. in size. It is of interest that the vesicles in an individual occasionally displayed marked dissimilarity in appearance. One vesicle may be distended and cystic in appearance and the other completely normal. No congenital anomalies were found among these specimens The vesicle mucosa in 48 was smooth and glistening. In 2 cases the mucosal surfaces were dull and covered with a fibrinous exudate. Frequently the lumina contained a dark red gelatinous substance which on occasion was adherent to the mucosa. Obstruction of the seminal ducts could not be demonstrated in any instance.

The prostate glands were grossly enlarged in 64.5 per cent of the specimens. Most of the enlargements involved the lateral lobes. Hypertrophy of the middle lobe occasionally produced posterior displacement of the ejaculatory ducts. Periprostatic induration was infrequent, being present in only 2 instances, the

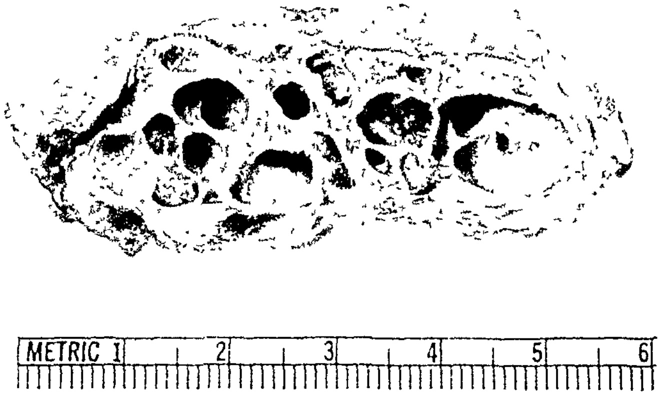

FIG 1 Greatly distended seminal vesicle Note presence of gelatinous material in some of outpouchings There was no evidence of inflammatory disease in vesicle. Case A52 143

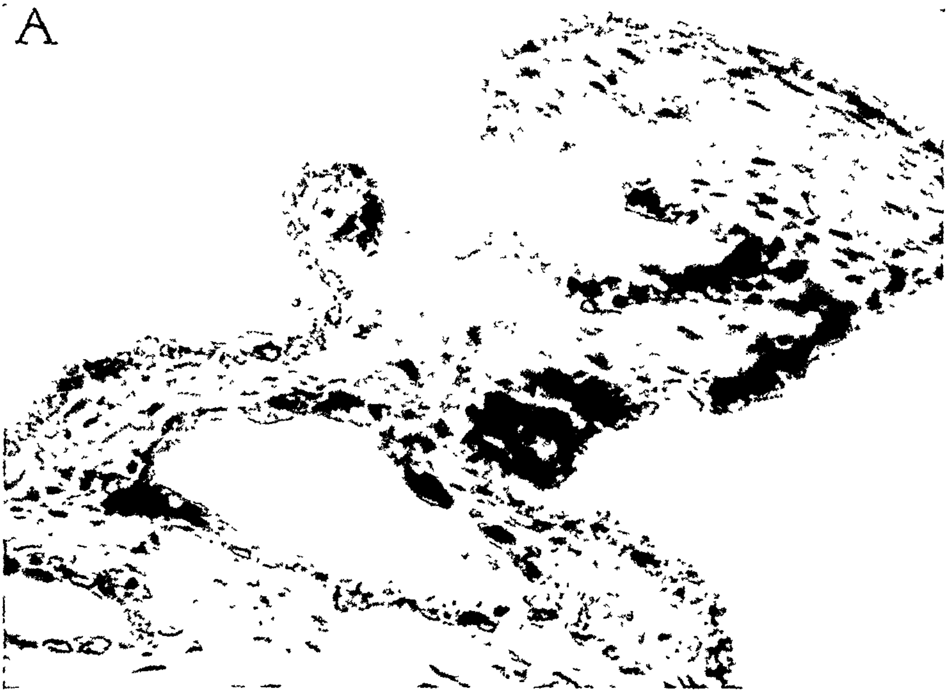

FIG. 2. *A*, Section of seminal vesicle of the case shown in fig. 3. No evidence of inflammatory disease in vesicle. Case A51-035.

prostatovesicular abscess and the prostatic carcinoma, which were mentioned previously.

Microscopic examination revealed that in 148 of the 161 cases the seminal vesicles were entirely free of inflammatory disease (fig. 2, *A*). Only 2 cases showed inflammatory cells within the lumen of the vesicles. These were the cases which earlier had shown perivesicular induration and dullness of the mucosa. Three cases revealed mild or minimal round cell infiltration of the wall of the vesicles and were associated with carcinoma of the prostate gland. The remaining 8 cases revealed minimal vascular or perivascular lymphocytic infiltration which was localized in the serosa or in the surrounding fascial structures.

The mucosa of the vesicles demonstrated hyperplasia in 75 cases and atrophy in 69. It is of interest that concretions resembling corpora amylacea were present in 7 seminal vesicles. There was an associated serosal perivascular round cell infiltration in 2 of these instances. The submucosa in most instances revealed varying degrees of fibrosis.

The vesicle muscularis varied in thickness, depending upon the presence or absence of dilatation and on the proportion of smooth muscle to fibrous tissue. Frequently the fibrosis was extensive but in no case did it completely replace the musculature. The fibrous proliferation began in the submucosa and extended outwardly toward the serosa. There were 2 instances of calcification within the vesicle muscularis, one of which revealed minimal chronic inflammation and the other none at all.

Vascular sclerosis in the seminal vesicles was a frequent finding and often was more marked than in the corresponding prostate gland.

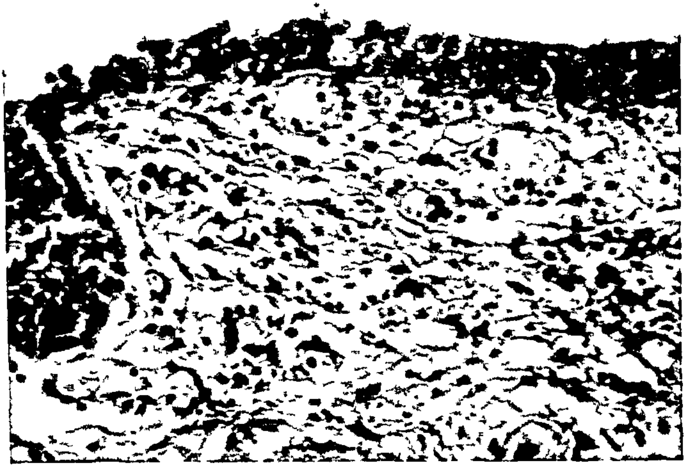

FIG 3 Diffuse lymphocytic infiltration in submucosa of ejaculatory duct This is at level of verumontanum Case A51 035

Microscopic evidence of inflammatory disease was present in 147 (91 3 per cent) of the 161 prostate glands It occurred either in the form of periacinar round cell accumulations or in groups within the fibromuscular stroma Adenocarcinoma occurred in 10 cases Fibrosis of the prostate, either generalized or focal, was very common and occurred both in the presence and absence of inflammation The fibrous proliferation was present to a greater degree and extent in the older age groups Infarction of the prostate was always accompanied by localized inflammatory reactions Inflammatory reactions of the urethra were present in 129 (80 1 per cent) of the cases Of these, 101 were mild or minimal and 28 were moderate to severe inflammatory reactions (fig 3) The ejaculatory ducts disclosed evidence of *inflammatory disease in 95 instances* Of these 72 were mild or minimal involvements, and 23 showed moderate to marked inflammation Although round cells were found in the mucosa of the urethra and the ejaculatory ducts, the preponderance of inflammatory cells was in the submucosa Perivascular lymphocytic infiltration was present but was not a prominent feature in the usual inflammatory process

REVIEW OF LITERATURE

In a review of the literature since 1918, only 5 studies of the histopathologic characteristics of the seminal vesicles have been found Of these 4 cite evidence of detailed examinations In 1923, Dillon and Blaisdell, on macroscopic examinations for the most part, classified the pathology of the seminal vesicles into 4 broad groups This classification depended upon the presence of ejaculatory duct obstruction and perivesicular inflammation which was said to result in adhesions about the vesicles. Eventually, the end result was said to be an atrophic vesicle, encased in a thick scar of such extent as to often make the vesicle hard to recognize. These authors also claimed that marked leukocytic infiltration and small abscesses may form in the perivesicular tissues. Habuto[4] (1929) published his observations in a purely histologic study of the seminal vesicles. In it he attempted to correlate the changes in cellular structure and the appearance of pigment with age, but gave no detailed references to pathological processes. Gutierrez[5] (1929) summarized his findings after having performed 100 consecutive seminal vesiculectomies in a search for focal inflammation as the cause of systemic diseases. Grossly, he noted the presence of frank pus in 2 instances and in some cases he noted that the vesicles were adherent to the posterior wall of the bladder and to Denonvilliers' fascia. While admitting that his microscopic examinations were incomplete, he found that many leukocytes and round cell infiltrations were present.

An extensive effort to define the pathology of the seminal vesicles was made by Hyams, Kramer and McCarthy in 1931. They reviewed 84 postmortem cases which were selected from a group of over 500. These cases were chosen because on inspection there appeared to be inflammatory disease of the urinary bladder, the prostate gland or the seminal vesicles. On the basis of their examinations, they refuted Dillon and Blaisdell's findings of perivesicular adhesions, having found only 6 cases of perivesiculitis and terminal fibrosis in over 500 dissections. Essentially theirs was a histopathologic study in which an attempt was made to correlate inflammatory disease of the prostate and posterior urethra with seminal vesiculitis. Their descriptions of the prostate gland emphasized inflammation involving the verumontanum and the ejaculatory ducts. This was said to be more likely to spread along the mucous membranes and cause seminal vesiculitis. Their criteria for the pathologic diagnosis of seminal vesiculitis were as follows: inflammatory cells must be found within the lumen, in the mucosa and submucosa, or between the mucous folds. They considered perivascular infiltrates in the fascial planes to be part of the vesicle inflammatory process. Only in cases of severe destructive prostatic and periprostatic suppration did they observe the muscularis of the seminal vesicle to be involved. Furthermore, they stated that vesiculitis did not exist without inflammatory disease in the ejaculatory ducts. Of their 84 cases, 16 revealed evidence of "marked chronic, subacute or acute vesiculitis." Thirty cases revealed "slight, indefinite catarrhal vesiculitis." Thirty-eight of their cases disclosed no evidence of inflammatory disease of the vesicles.

Herbst and Merricks[6] (1940) stated that blocked ejaculatory ducts convert the vesicles into infected retention cysts or chronic abscesses. They further claimed that failure of treatment of so-called chronic prostatitis was due to persistent seminal vesiculitis.

[4] Habuto, E.: Uber die Veranderung der Samenblase durch Lebensjahre. Ztschr. f. Urol., **23:** 916–966, 1929.

[5] Gutierrez, R.: Later results of surgery of the seminal vesicles. Tr. Sect. Urol. A.M.A., pp. 194–226, 1929.

[6] Herbst, R. H. and Merricks, J. W.: Transurethral approach to the diagnosis and treatment of infections of the seminal vesicle. Ill. M. J., **78:** 393–397, 1940.

According to Harlin[7] (1950), in the chronic phase of the inflammatory process, the entire thickness of the vesicle wall and the ampulla are involved He also stated that the vesicle was eventually reduced to a fibrous cord or to a multiloculated pus sac

DISCUSSION

Observations made during this study concur in part with those of Hyams Perivesiculitis and perivesicular adhesions are rare, and the muscularis of the seminal vesicles is invaded by inflammatory cells only in the presence of destructive suppuration of the prostate gland or the periprostatic tissues However, the results of this study disagree with Hyams' conclusion that seminal vesiculitis commonly coexists with inflammation of the ejaculatory ducts The incidence of inflammatory reactions of the ejaculatory ducts is almost identical in both studies However, I found no correlation between seminal vesicle and ejaculatory duct inflammation This is in contrast with Hyams' findings of seminal vesiculitis in 46 of 49 cases which revealed evidence of inflammatory reaction in the ejaculatory ducts

Further analysis of Hyams' findings reveals that 16 of his specimens show evidence of marked inflammation of the vesicles Of these only 4 show definite inflammation of the vesicle wall Two of these were secondary to prostatic or periprostatic abscess and 2 were instances of "marked, chronic catarrhal seminal vesiculitis " Thus, among his 84 selected cases he mentions only 2 instances of severe inflammatory disease of the seminal vesicles not associated with suppuration within or about the prostate gland The remaining 30 instances of seminal vesiculitis are ambiguously described as "slight, indefinite and catarrhal " It would seem that the proper interpretation would be that seminal vesiculitis ordinarily occurs only in the presence of prostatic or periprostatic suppuration

My observations disclose the presence of marked inflammatory reaction in the seminal vesicles in only 2 of 161 cases These were associated with prostatic abscess and with adenocarcinoma of the prostate Minimal inflammation of the vesicle wall was noted in 3 cases, each associated with prostatic carcinoma Eight of my specimens revealed isolated vascular or perivascular round cell accumulations which were localized in the serosa or in the surrounding fascial structures Four of these are associated with adenocarcinoma of the prostate Three infiltrates are due to periarteritis nodosa (fig 4), generalized arteritis and leukemia The one remaining instance of perivascular infiltration cannot be accounted for Thus, these observations indicate that when vesiculitis is present, it is usually associated with prostatic carcinoma or suppuration Furthermore, they reveal that inflammation of the seminal vesicles is not necessarily associated with inflammatory disease of the posterior urethra and ejaculatory ducts

No evidence was found to support Dillon and Blaisdell's contention that abscess formation and thick scars develop around the seminal vesicles and that total fibrosis of the vesicles is the end result In attempting to explain their findings, it might be conceded that 1) suppurative inflammations of the seminal vesicles and the prostate gland were more common at the time of his study, and

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[7] Harlin, H C Seminal vesiculitis J A M A , 143 880-884, 1950

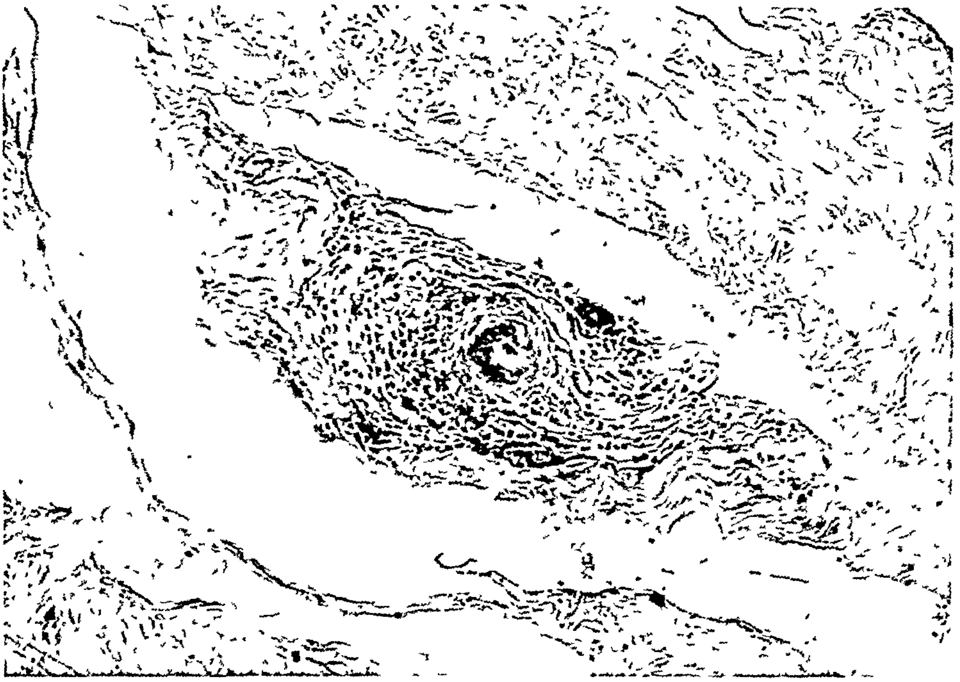

FIG. 4. Perivascular round cell infiltration due to periarteritis nodosa and localized in serosa of seminal vesicle. Case A52 030.

2) that present day use of sulfonamides and antibiotics has reduced the incidence of suppuration. Since my findings also contradict those of Gutierrez, perhaps the same reasons can be offered in explanation of the differences.

However, Harlin's conclusions were made recently. His statements that the vesicles were reduced to fibrous cords or to multiloculated pus sacs are completely unsupported by my findings. Furthermore, he has submitted no pathological evidence to substantiate his conclusions. Thus, any attempt on my part to discuss them would be speculative.

It is an accepted fact that one of the end stages of inflammation is fibrosis. However, all fibrosis is not a result of inflammatory disease. A good deal of it, perhaps more than we realize, is a replacement type of fibrosis which occurs in certain pathologic processes and with advancing age. We see examples of this in the fibrosis of the uterus, in the fibrous proliferation of the prostate and in the walls of blood vessels. No claims have been made, to my knowledge, that these instances are due to inflammatory disease. In the absence of evidence which can explain the mechanism of this fibrous proliferation in the seminal vesicles, it is difficult to ascribe it to inflammation. It is more likely than not a replacement type of fibrosis which accompanies advancing age. In order to brand it an end result of an inflammatory reaction, there should be more evidence of inflammation and not merely conjecture.

Judging from the amount of literature published, the clinical diagnosis of chronic seminal vesiculitis has been made frequently[8-24] but Singer[25] (1946)

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[8] Fraser, A. R and Goldschmidt, L B : Surgical management of seminal vesiculitis. Lancet, 2: 749-751, 1926.

cautioned that many errors are made in the diagnosis of vesiculitis Many have associated seminal vesiculitis with chronic prostatitis A great deal of stress has been placed on the finding of pus cells in the seminal fluid and the assumption has been made universally that at least part of these pus cells came from the vesicles Bacteriologic studies have been made of seminal fluid, but none of these examinations appear valid. A method will have to be devised whereby fluid can be obtained directly from the vesicles without contamination in order for bacteriologic studies to have meaning Transurethral methods fail in this respect

CONCLUSIONS

A histopathologic search was made for evidence of inflammatory disease of the seminal vesicles in 161 routine autopsies The results of these examinations lead to the following conclusions:

Histopathologic evidence of chronic seminal vesiculitis is rarely observed When seen, inflammatory disease of the vesicles is not necessarily associated with inflammation involving the prostate gland, urethra or ejaculatory ducts

In this study, inflammatory reactions of the seminal vesicles commonly accompanied prostatic carcinoma, prostatic or periprostatic abscess

Perivesiculitis and perivesicular adhesions were rare and occurred only in the presence of severe destructive suppuration of the prostate gland or periprostatic tissues

Replacement fibrosis of the seminal vesicles was common and often extensive, but not sufficient to completely replace the vesicle muscularis or to obliterate the lumina. This fibrous proliferation is considered to be part of the aging process and not the end result of inflammatory disease

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VOLUME OF IRRIGATING FLUID TRANSFER DURING TRANSURETHRAL PROSTATECTOMY, STUDIED WITH RADIOISOTOPES

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Intravascular hemolysis,[1] toxic symptoms,[2] transient bacteremia,[3] osteomyelitis,[4] overhydration,[5] hyperglycemia[6] have been reported as being due to the transfer of irrigating fluid into the vascular system of man during transurethral prostatectomy. Despite the frequent performance of the operation in this country, the report of Landsteiner and Finch,[7] in which sodium salicylate was used to label the irrigating fluid in 3 cases, was the only quantitative study of irrigating fluid transfer which we found in the literature.

It would appear that the volume of irrigating fluid transferred into the patient's bloodstream might be as important a consideration as the type of fluid used in transurethral prostatectomy. The importance of the type of irrigating agent selected is reflected in the hospital mortality experience of one of us (Griffin). Among the first thousand cases of transurethral prostatectomies using sterile water as the irrigating agent, 6 deaths occurred (six tenths of one per cent). Two of these were due to anuria. Of the last five hundred cases subjected to the operation, using 4 per cent glucose for an irrigant, there has been 1 death (one fifth of one per cent). This patient died on the operating table of coronary occlusion.

Accurate determination by volumetric means is difficult when the operation is performed with the McCarthy type of resectoscope, for some fluid may be lost as the lens system is withdrawn from the sheath for aspiration of the bladder contents. This determination is feasible, however, when the Thompson cold punch is used because the outlet valve may be opened without disrupting the visual system. Radioisotope techniques offer other means for determining fluid transfer in clinical cases. As a pilot study, both volumetric and isotope methods were applied to a small group of the common types of prostatic obstruction subjected to transurethral operation. Cases from each of the general classes of large, moderate and small prostates were chosen for diversity in size. Variation

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Read at annual meeting, American Urological Association, Los Angeles, Calif., May 16–19, 1955.

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in pathology was obtained by including benign prostatic hyperplasia, adenocarcinoma of the prostate and fibrotic contracture (primary and postoperative) Two cases of prostatic calculi with fibrotic prostatitis were included because it is generally recognized that the stones usually lie near the capsular region where veins and sinuses are often cut

METHODS

Volumetric Twenty liters of 4 per cent glucose solution were prepared as irrigation fluid for each patient, and measured volumetrically before surgery Use of a closed irrigating system and the Thompson resectoscope prevented loss of fluid onto drapes during surgery

The unused portion of irrigating fluid and return irrigating fluid containing blood lost and urine excreted during surgery were again measured volumetrically The additional water necessary to bring the total back to the original volume was taken as the volumetric determination of fluid transferred into the patient Volumes were measured with a graduated cylinder and volumetric flasks In the cases with the three largest prostates, the hemoglobin content of the return fluid was determined photoelectrically and this correction applied to the volumetric determination

Radioisotope Fluid transfer was studied in these patients also by labeling the irrigation fluid with radioactive tracer and determining the amount of tracer appearing in the blood stream

In the first 3 cases (D C , E C and C C) the irrigant was labeled with I^{131} as sodium iodide to a level of twenty microcuries per liter Blood samples were taken at intervals during and after surgery, and determinations made of the radioactivity of whole blood and of plasma by means of a well type scintillation counter The irrigant was counted in the same way *In vivo* counting was carried out over the thyroid glands 48 hours after surgery and correction was made for the very small amount of I^{131} deposited there These patients had been given KI to block thyroid uptake of radioiodine

In these three cases the tracer was in the form of a freely diffusible ion with a high concentration gradient between irrigant and tissue fluids and could therefore not be used to directly measure fluid transfer The quantity of tracer which appeared in the patient was taken however, as an indication of the "exposure" of the patient to the irrigant This "exposure" thought of as being determined by such things as the concentration gradient and diffusion coefficient of the iodide ion, extent of contact between opened tissue and irrigant, duration of contact and irrigant pressure, was determined in these patients as a preliminary step in the study 'Exposure" was expressed arbitrarily as cubic centimeter of irrigant containing the amount of radioiodide found in the patient after surgery

Measurements of blood samples indicated that the radioactive iodine distributed itself in blood cells and plasma in the ratio 40 per cent to 60 per cent Assumptions were made for the purposes of computations presented here that a) the I^{131} concentration in extracellular fluid (taken as 15 per cent of the body weight) is in the same ratio to that of extracellular fluid as that of blood cells to plasma

On the basis of these considerations the body content of I^{131} after surgery was computed from blood sample data. The amount of I^{131} thus determined when divided by the concentration of I^{131} in the irrigant gives the "exposure"—the volume of irrigant originally containing the amount of I^{131} which was found in the patient.

In the last 4 cases (J. M., M. K., H. N. and O. K.) the irrigating fluid was labeled with radioiodinated human serum albumin to a level of ten microcuries per liter. Blood samples were taken at intervals during and after the operation for radioassay.

In the last three of these patients blood volume measurements were made before surgery by means of an earlier intravenous injection of radioiodinated human serum albumin.

Because of the large size of the albumin molecule and the known slowness with which this substance leaves the vascular system, fluid transfer was computed by taking the body content of tracer as the product of blood volume and blood concentration of I^{131}-albumin. This value divided by the concentration of label in the irrigant gives the volume of irrigant which must have been transferred into the patient's bloodstream.

In patients whose blood was labeled before surgery for blood volume measurements, a value determined by extrapolation of pre-surgery data was subtracted from the post-surgery blood concentration figure to give the change in I^{131}-albumin level induced by the operation. This value was multiplied by the blood volume to give the total amount of tracer gained by the patient during surgery. This amount divided by the irrigant concentration of tagged albumin gives the volume of irrigant transferred.

TABLE 1

Patient	Diagnosis	Prostate Removed grams	Blood Loss cc	Irrigating Fluid Volume Difference cc	"Exposure" cc Irrigant	Irrigant Transferred into Patient, cc	
						Fluid volume method	I^{131} albumin method
D. C., No. 1693F	Prostatic fibrosis & calculi	14	**	700	475	700*	
E. C., No. 1706F	Benign prostatic hypertrophy	150	780	3,170	4,000	3,950*	
C. C., No. 1846F	PO vesical neck contracture	18	**	370	440	370*	
Z. S., No. 2085F	Median prostatic bar	20	**	400		400*	140
M. K., No. 3619F	Carcinoma of prostate	35	570	505		1,075*	315
H. N., No. 3913F	Prostatic fibrosis & calculi	15	**	550		550*	0
O. K., No. 3964F	Benign prostatic hypertrophy	62	620	830		1,450*	220

* Plus unknown volume of urine excreted, and in ** blood lost into irrigant.

TABLE 2

Patient	Weight kg	Hematocrit	cpm/cc Plasma	cpm/cc RBC	cpm/cc Irrigant
D. C.	65.8	50	248	189	12,500
E. C.	72.7	53	1,291	802	12,400
C. C.	63.2	46	174	109	13,400

TABLE 3

Patient	Blood Volume, Liters	cpm/cc Blood After Surgery	cpm/cc Blood Extrapolated	Change in cpm/cc Blood	cpm/cc Irrigant
Z. S.	*	148	0	148	4,842
M. K.	5.06	1,140	654	486	7,790
H. N.	6.07	693	693	0	5,338
O. K.	5.93	2,050	1,660	390	10,546

* Assumed 8% of body weight.

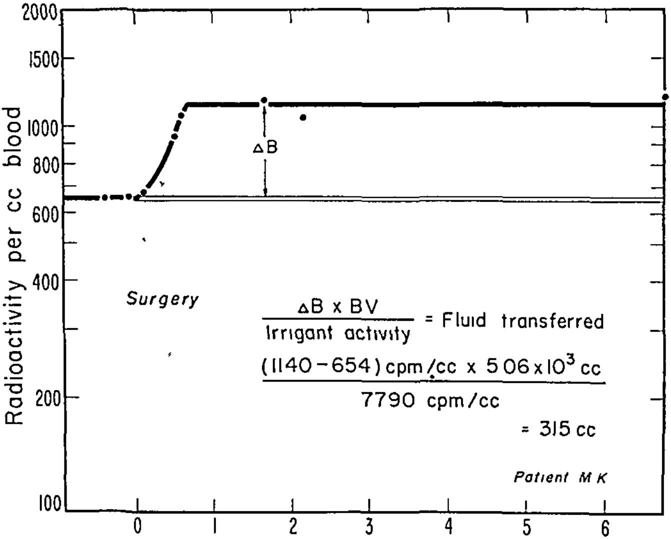

FIG. 1

RESULTS

In all cases a significant amount of fluid transfer was found by the volumetric method, the amount varying widely from the smallest (370 cc) to the largest (3,950 cc). Three of these values were corrected for blood content of the return irrigant. It should be noted that the uncorrected values as they appear in the remaining cases might be expected to be low by the volume of blood actually lost into the irrigant. Also, the values in all cases do not take into consideration the unknown quantity of urine excreted by the patient during the operation. In table 1 is given the measured volume difference for each patient and, with blood loss corrections, the volumetrically determined fluid transfer.

In table 2 are listed the I^{131} activities measured in plasma, in red cells, and in the irrigating fluid for the first three patients who were studied with NaI^{131}-labeled irrigant. Also shown in the table are hematocrits and body weights. From these numbers computations of body I^{131} content and "exposure" were made as outlined above. Values for "exposure" appear under this heading in table 1.

Concentrations of labeled albumin in whole blood as counts per minute per cubic centimeter are given in table 3 for the last four patients who were studied with this material. Blood volumes are also given for three of them, these volumes having been done before surgery with the labeled albumin technique. Fluid transfer computed as indicated in the section on Methods, is shown in table 1.

Data from patient M. K. are shown in figure 1 to illustrate the rise in labeled albumin which accompanied surgery.

DISCUSSION

Regardless of whatever reasonable error might exist in the volumetric measurement, it seems irrefutable that an amount approaching four liters can be transferred during prostatic surgery. However, it should be pointed out that neither the number of cases nor the character of this study permits interpretation of results as being typical of what happens in clinical practice on similar cases. In this regard, it should be emphasized that the cases selected were in good physical condition, and wide excision of tissue under high water pressure without undue surgical risk was intentionally carried out in an effort to obtain maximum figures of fluid transfer.

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It is of interest that the arbitrary expression of irrigant "exposure" in terms of cc irrigant giving up iodide to the patient gives numbers rather close to the volumetrically determined fluid transfer. Although this may derive from the assumptions made in the computation and be fortuitous, it suggests that further investigation of this point might be of value. It is apparent that the relative proportions of the iodide ion and water transferred to the patient will vary with the mechanism of transfer In the presence of the driving force of a high hydrostatic pressure and many open blood vessels in the operative site, the proportion of label to fluid transferred tends to approach the proportion in the original irrigating fluid When the fluid transfers primarily by diffusion in the operative site, iodide ion and water may be expected to move more independently A double marking of the irrigant with both a diffusible and nondiffusible label would be a reasonable approach to the study of this question

The albumin data are interesting in comparison with the other as they substantiate the hypothesis that irrigating fluid is transferred in significant amounts, both extravascularly and by way of open vessels in the operative site The albumin method failed to show any transfer into vessels in the case of patient H N , while more than 300 cc were so transferred in patient M K It seems likely that a larger series of patients studied in this manner would show a much wider range

It is difficult in terms of mortality or morbidity statistics to evaluate the importance of the volume of fluid transfer However, such time honored principles in transurethral surgery as low water pressure, frequent emptying of the bladder and short duration of operating time are emphasized by the quantitative data in our report Furthermore, our studies suggest that the surgeon's clinical impression of the vascular sinuses and veins that are opened during the operation and the amount of fluid that is being transfused is of significant value Obviously the infusion of large quantities of fluid in the range of 3,000 cc, as found in the case of E C , might be a fatal factor in a patient with poor cardiac reserve Our study tends to support the hypothesis that infusion through the veins of the prostatic capsule might be as important a factor as infusion of fluid through the peripheral veins of the postoperative patient in cases of over hydration, as described by Bulkley, O'Conor and Sokol [5]

SUMMARY

This preliminary study indicates that significant quantities of irrigation fluid may be transferred into patients during transurethral prostatectomy

The volume transferred varies widely in different patients and may be large enough to cause untoward clinical effects

The tracer use of radioactive I^{131} as iodide and as I^{131}-tagged human serum albumin to label the irrigation fluid was of value in measuring the volume of fluid transferred

Evidence is presented indicating fluid transfer is both extravascular and by way of open vessels

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SPERM MOTILITY: A SIMPLE METHOD FOR ANALYSIS

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As early as 1868 Sims[1] suggested three major points for determination of sterility and fertility: 1) whether the semen contained spermatozoa; 2) whether the semen entered the cervical canal; 3) whether the uterine discharges were favorable to the life of the spermatozoa, i.e., impregnation. Since that time investigators of fertile and infertile groups have studied semen specimens, and more particularly the spermatozoa, with varied and diverse results, estimating total count, morphology, proportion of live to dead cells, survival time, motility and action in endocervical secretions.[2-12] MacLeod has stated the need for estimating sperm "quality".[13] This is apparent to 'trained observers' but difficult to transmit quantitatively from one trained observer to the other.

An ideal method for observation of motility would be direct observation of the vaginal-uterine-tubal tract in man. The impracticality of this makes necessary studies with close approximations, including similar geometry, cervical mucus and unaltered semen. The necessity for sorting spermatozoa brings to the fore the issues of gravity, increased viscosity and refrigeration as aids for a differential sperm study.

The use of capillary tubes as an aid to the observation of semen and cervical mucus was described by Lamar, Shettles and Delfs.[14] They used a small amount of mucus, then a small air bubble to prevent mechanical mixing, then a column of fresh semen in capillary tubes 0.10 to 0.40 mm. inside diameter. This separation by an air bubble of mucus and semen for the purpose of preventing mechanical mixing gave an added, immeasurable artifact to all observations. In spite of this air bubble barrier for the sperm, they found relatively easy penetration by spermatozoa; in some cases spermatozoa had a short invasion period and then stopped. Abarbanel[15] put cervical mucus in one capillary tube, semen in a

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[15] Abarbanel, A.: Cervical mucus changes. Trans. Am. Soc. for Study of Sterility, pp. 46–60, 1946.

smaller tube, and introduced it into the mucus capillary. This method raises the questions of mechanical mixing and instability for microscopic observations. He reported, however, that only 1 in 100 spermatozoa penetrated, normal and abnormal alike. He found that sperm were active longer in mucus than at room temperature; progression in mucus was 2.5–4.0 mm. per minute. Page and Houlding[16] reported that Hamman of Denmark followed motility in specimens sealed with paraffin in capillary tubes and described average endurance time in excess of 3 days. Gamble[17] reported in 1953, after the present work had started, that capillary tubes kept in a horizontal position had been used to observe the *immobilizing power of contraceptive jelly.* The horizontal position in this, as in other observations to date, fails to take advantage of the gravitational aspects of the problem.

The present investigations were conducted in an effort to establish a stable, reproducible method for measuring the motility of spermatozoa under conditions that resemble those that take place in the human body. Semen specimens have been observed in an effort to determine, at body temperature, the rate of progression of spermatozoa in relation to the percentage of motility, and to analyze the pattern of motility in a variety of specimens.

There are several factors that make the present observations approximations rather than duplications of physiological processes: 1) the glass tube as a container differs from the vaginal cavity, 2) there are no white blood cells to aid in maintaining a bacteria-free atmosphere for sperm, 3) there is the danger of mixing. In addition, the technique, when first used, is time-consuming.

METHOD

A. Ringer's solution and semen. Specimens observed were obtained from volunteers aged 22–33 years in good health, and from patients aged 22–42 years with known problems of infertility. The ratio of specimens from presumably fertile subjects to those from subjects with problems of infertility was 6:1. A total of 124 observations were made of 75 samples. In 104 observations morning specimens were put in sterile glass containers, covered, and examined under microscope within 1–3 hours. Twenty observations were made after the specimens had been refrigerated 12–48 hours. Continence of 3 days was requested; in 14 observations 2-day continence was reported, and in 5 observations there was 5-day continence.

Experimental comparative counting methods used in these estimates have been based on techniques recently described[18, 19] with one variation. The pipette containing semen and Ringer's solution was placed in a Burton pipette shaker

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SPERM MOTILITY: A SIMPLE METHOD FOR ANALYSIS

ROBERTA SCHWARTZ AND H. H. ZINSSER

As early as 1868 Sims[1] suggested three major points for determination of sterility and fertility: 1) whether the semen contained spermatozoa; 2) whether the semen entered the cervical canal; 3) whether the uterine discharges were favorable to the life of the spermatozoa, i.e., impregnation. Since that time investigators of fertile and infertile groups have studied semen specimens, and more particularly the spermatozoa, with varied and diverse results, estimating total count, morphology, proportion of live to dead cells, survival time, motility and action in endocervical secretions.[2-12] MacLeod has stated the need for estimating sperm "quality".[13] This is apparent to 'trained observers' but difficult to transmit quantitatively from one trained observer to the other.

An ideal method for observation of motility would be direct observation of the vaginal-uterine-tubal tract in man. The impracticality of this makes necessary studies with close approximations, including similar geometry, cervical mucus and unaltered semen. The necessity for sorting spermatozoa brings to the fore the issues of gravity, increased viscosity and refrigeration as aids for a differential sperm study.

The use of capillary tubes as an aid to the observation of semen and cervical mucus was described by Lamar, Shettles and Delfs.[14] They used a small amount of mucus, then a small air bubble to prevent mechanical mixing, then a column of fresh semen in capillary tubes 0.10 to 0.40 mm. inside diameter. This separation by an air bubble of mucus and semen for the purpose of preventing mechanical mixing gave an added, immeasurable artifact to all observations. In spite of this air bubble barrier for the sperm, they found relatively easy penetration by spermatozoa; in some cases spermatozoa had a short invasion period and then stopped. Abarbanel[15] put cervical mucus in one capillary tube, semen in a

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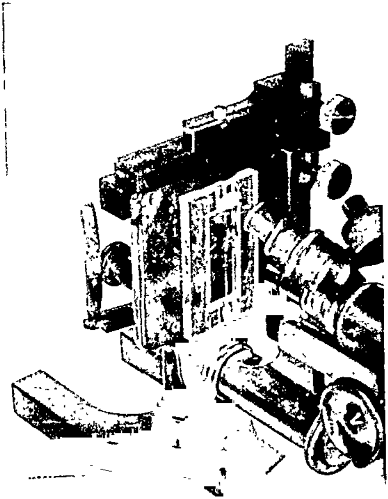

FIG. 1. Microscope in horizontal position with capillary tubes in holder in vertical position in mechanical stage.

ward progression of the sperm. An increase or decrease in motile power, in the number of active and inactive spermatozoa, in granulation, crystallization and disintegration could also be observed.

As a preliminary to these tests, capillary tubes were filled in the manner described with Ringer's solution and a saturated solution of pontamine blue dye. The dye diffused upward at average rate of 1.6 mm. in 2 hours. Dye diffusion in cervical mucus was 1.4 mm.

B. Cervical mucus and semen. Freshly aspirated cervical mucus from 17 women of presumed or proven fertility was drawn into capillary tubes as previously described, sealed with beeswax, and centrifuged for 25 minutes at 3000 r.p.m.'s. Centrifusion was carried out in order to move the mucus to the far, sealed end without an air bubble. This did not separate the cellular elements. A glass tube, drawn to a fine point over flame, was filled with semen; the semen was carefully blown into the open end of the capillary tube containing the centrifuged mucus. Care was taken that no air bubble separated the semen and mucus, and that no or a minimum of mixing occurred. The tube was placed in a vertical position on a glass slide and held in place with scotch tape. Microscopic observations under oil immersion were made as previously described, and the top sperm position noted at 0 hour and 2 hours, with the tube maintained in a vertical position and kept at body temperature between observations; the difference in the two figures denoting the progression and penetration of the cervical mucus by the spermatozoa.

Spermatozoa penetrated singly, and did not seem to follow the path of the previously observed sperm. Spermatozoa that penetrated cervical mucus did not deteriorate as rapidly as sperm in Ringer's.

RESULTS

Statistical data are presented in table 1.

Progression in Ringer's solution in 104 observations of 60 samples showed penetration of 6.5 mm. with a standard deviation of 2.98. Duplicate observations of the same semen specimen in Ringer's solution showed a standard deviation of 1.76 mm.

In 25 observations of 17 cervical mucus specimens the average penetration by semen specimens which had motility over 25 per cent was 7.5 mm. with a standard deviation of 5.8 mm. In duplicate observations of the same semen specimen in the same cervical mucus the standard deviation was 1.4 mm.

When the per cent of living spermatozoa was over 60 per cent, there was upward progression in the capillary tubes; when under 30 per cent there was downward progression in the capillary tubes; between 30–60 per cent there was upward progression in the ratio of 10:8. Three tests showed inconsistency with the

TABLE 1. *Progression in millimeters*

Description	% Motile	Count Millions/cc	Number Samples	Number Observation	2 Hour Progression	Standard Deviation
Ringers & semen Over 25% motile	56	140	60	104	6.5	2.983
Cervical mucus and semen Over 25% motile	57	108	17 Cerv. mucus 12 Semen	25	7.5	5.8
Ringers & semen Over 25% motile refrigerated	31	117	7	9	3.6	2.839
Ringers & semen Under 25% motile refrigerated	10	97	8	11	−2.2	3.6
Ringers & semen fertile	60	146	25	40	6.6	3.2
Ringers & semen unspecified	60	138	23	42	7.0	3.0
Ringers & semen infertile	38	108	12	22	5.1	2.74
Cervical mucus fertile	64	133	8 Cerv. mucus 5 Semen	12	5.5	5.26
Same specimen Duplicate observ. in Ringers	53	133	28	56	Difference in progression 2.1	1.76
Same specimen Duplicate observ. in Cervical mucus	76	110	4	8	Difference in progression 0.7	1.40
Same specimen Duplicate observ. in Different cerv. mucus	50	90	10 Cerv. mucus 5 Semen	13	Difference in progression 3.3	3.6

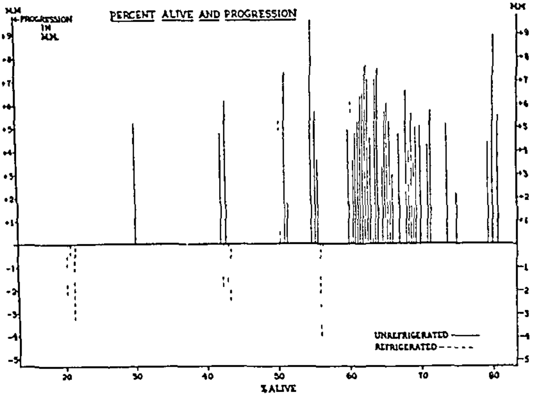

FIG. 2. Per cent alive and progression

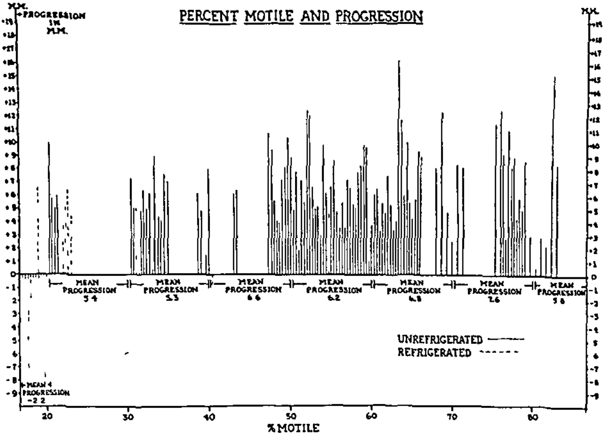

FIG. 3. Per cent motile and progression

per cent motile, due either to an error in staining or a chance congestion of dead sperm; a repeat test demonstrated the inconsistency (fig. 2).

Refrigerated specimens with over 25 per cent motility showed upward progression in all but one case. Refrigerated specimens with under 25 per cent motility showed downward progression in all but one case.

Fresh specimens with over 25 per cent motility showed uniform upward progression in Ringer's solution (fig. 3) and in cervical mucus. Standard deviation in cervical mucus, however, was twice as great as in Ringer's solution. Duplicate observations of cervical mucus showed a slightly smaller standard deviation than did those in Ringer's.

In the small sampling to date, penetration and progression of spermatozoa in cervical mucus were not restricted to any particular period in relation to the time of menstruation (fig. 4). Distance progressed was not consistent within any one day of the menstrual month, nor for any particular day or group of days.

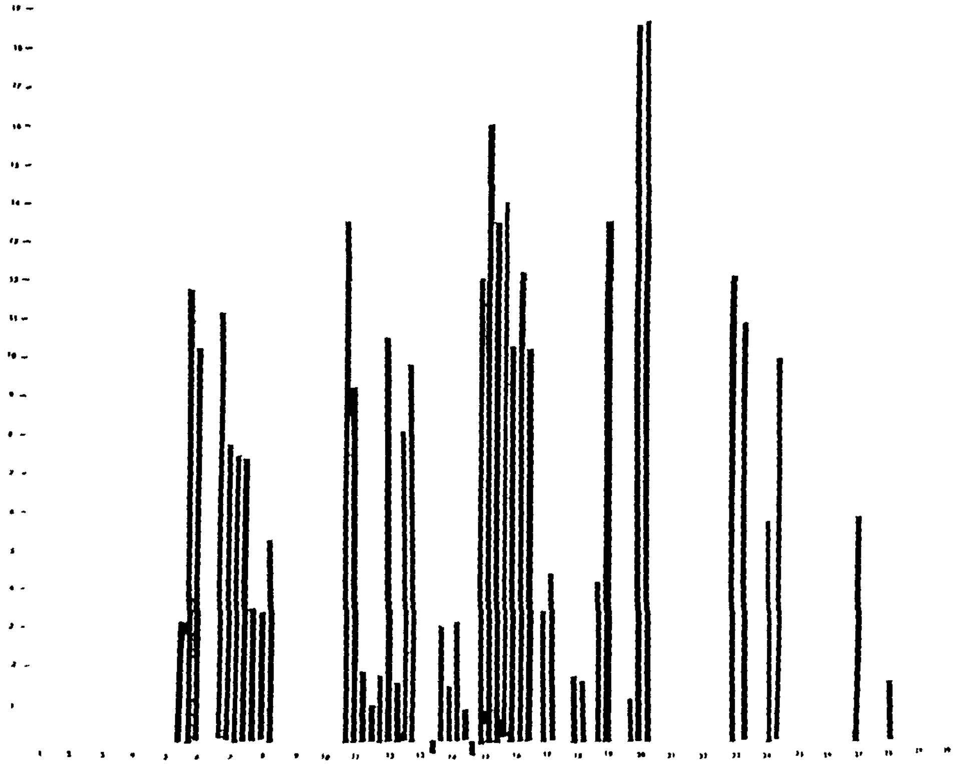

FIG. 4. Progression of sperm in cervical mucus according to day of menstrual month

CONCLUSIONS

At all times upward and downward progression was consistent in one direction or the other at the 1-hour and 2-hour observation.

There was no apparent relation between count/cc and progression.

There was correlation between per cent of motility and direction of progression; upward over 25 per cent motile, downward under 25 per cent motile. There was no correlation between motility or proven fertility and distance of progression.

Duplicate observations of the same semen specimen in Ringer's solution yielded a standard deviation of 1.76 compared to 2.98 in the general population. Duplicate observations of the same specimen in cervical mucus showed a standard deviation 1.4, but the general deviation was twice as great as in Ringer's solution.

There was correlation between per cent of live spermatozoa and direction of progression; over 60 per cent alive progression was always upward, below 30 per cent alive it was always downward.

Extension to infertile groups may yield data as to effectiveness of therapy in assisting spermatozoa to fertilize *in vivo.* Contraceptive materials can be quantitated in their capacity to inhibit penetration and migration through cervical mucus quantitatively.

SUMMARY

It is believed that a simple method has been found to measure the upward and downward progression of spermatozoa at body temperature, which is adapted to the study of spermatozoa in cervical mucus to determine whether essentially simple findings of sperm motility in seminal fluid, kept at body temperature, can be transferred to a prediction of their behavior in secretions of the female genital tract. Values for 104 observations for 12 infertile, 25 fertile, and 23 unspecified specimens are listed in Ringer's solution. These are shown to correlate well with progression in cervical mucus. The standard deviation in Ringer's is, however, ower than that in cervical mucus.

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THE EVOLUTION OF WATER CASTING

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> 'These follies are within you and shine through you like the water in a urinal, that not an eye that sees you but is a physician to comment on your malady'.
> William Shakespeare
> (Two Gentlemen of Verona, Act II, Scene I)

One of the commonest methods of diagnosis in the Middle Ages and in later times was the so-called water casting—diagnosis of disease by inspection of the urine.[1] As the urine could be sent away to a famous physician, diagnosis at a distance was a common practice. In view of the importance attached to this procedure, we find that under the Jerusalem Code of 1090, deviation from this practice was made punishable by public scourging. Innumerable medieval pictures and sculptures show the doctor holding up the urine glass and gazing intently upon its contents. These masterpieces often reflect the physician's reaction as to the severity of the disease. One, in particular, depicts a consultant at the bedside of a dying patient who was unable to dissemble his alarm on gazing at the urine and dropped the urinal in dismay.

Certainly, the art of water casting has undergone a considerable change from the cursory visual examination of urine as here referred to. Today, it is possible to establish the existence of many types of pathologic and physiologic disorders in the body by virtue of the various tests and procedures that are concerned with water casting. Of special interest to us is the fact that we are now able to establish the existence of a urinary tract infection by microscopic identification of pus cells and bacteria, even so far as designating between various generic types, direct visual observations for the presence of uropathies, and x-ray which helps to locate the specific areas of involvement. In addition, we have available effective antimicrobial agents of great diversity, whose sphere of activity encompasses most of the pathogens involved in these infections. However, in spite of these advances in diagnosis and treatment, we cannot fail to be cognizant of certain definite limitations which still exist in the management of urinary tract infections. Obviously, this situation is incapable of improvement unless the factors contributing to the development of infections of the urinary tract, as well as those responsible for therapeutic failures, are known and understood. Unfortunately, at this time knowledge is not sufficient to permit a final and systematic analysis of these problems. Nevertheless, we may discuss briefly some of the basic principles involved in the management of urinary tract infections.

Read at annual meeting of Mid-Atlantic Section of American Urological Association, Atlantic City, N. J. April 15, 1955.

[1] Riesman, D.: The Story of Medicine in the Middle Ages. New York: Paul B. Hoeber, Inc., p. 328, 1935.

HOW DO URINARY TRACT INFECTIONS DEVELOP?

In general, infection anywhere in the body involves two living entities—the infectious agent and the host—the outcome of which depends ultimately upon the ability of the microbial parasite to grow and/or spread within the fluid and tissues of the host. This, in turn, is influenced by the virulence, numbers, and tissue adaptability of the infecting agent and the tissue resistance of the host. Although this explanation for the development of infection sounds simple, the fact is that it still remains a perplexing riddle. Consider, for example, that pathogens of all kinds can persist in an active form in the tissues of a susceptible host without causing detectable lesions. In fact, invasion of the body by bacteria is probably going on continuously, as a result of penetration of presumably intact barriers, such as the respiratory and gastrointestinal tracts. It is well established that bacteremias often follow such operative procedures as tonsillectomy, the extraction of teeth, and prostatectomy without producing any established infection in the body. However, these transient bacteremias are only of consequence when there is an associated abnormality, such as a congenital or acquired anatomic defect (e.g. a previously damaged heart valve) which leads to the establishment of a focal infection. However, under normal conditions, the parasite and host live peacefully together, or at least with no evidence of infection. It would seem, therefore, that in order for all men to live at peace at all times with microbial parasites, we should identify the factors which make it possible for so many individuals to harbor micro organisms endowed with pathogenic potentialities without manifestation of infection.

While there is little knowledge of the precise mechanisms by which latent infections can be converted into active disease, it seems apparent, from recent studies by Dubos,[7] that certain factors, such as nutritional, metabolic, and hormonal disturbances, play a role in the alteration of the metabolism of infected hosts. As an example of this, he points out that most micro organisms are taken up by phagocytic cells as soon as they are introduced into the body and later are released into extracellular environment of the necrotic lesion. These leukocytes, in turn, can produce large amounts of lactic acid and it is probable that the intracellular pH, following a phagocytosis, is rather low. Similarly, it is certain that the pH of inflammatory exudates is very acid, as a result in part at least of the local accumulation of lactic acid produced by inflammatory cells. Furthermore, *in vitro* suspensions of many bacterial species are sterilized more rapidly at acid reactions in media containing lactic acid, than in solutions containing other acids. Thus, lactic acid possesses antibacterial activity precisely under the conditions which normally exist in inflammatory areas, hence it acts as a natural antibiotic. In contrast to lactic acid, other substances accumulating at the site of a necrotic breakdown, such as keto acids, favor bacterial growth under the very same conditions and can antagonize to some extent the bactericidal effect of lactic acid. Suggested evidence of this relationship is found in the great susceptibility to infection associated with uncontrolled diabetes or

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Dubos, R. J. Biochemical Determinants of Microbial Diseases. Cambridge, Mass. Harvard University Press, 1954.

with acute starvation, in both of which instances ketosis is often present. In *both instances, the ensuing infections are easily controlled if the diabetic receives* adequate insulin or the starving individual is returned to a satisfactory nutritional state. Hormones, in their turn, can indirectly bring about profound changes in the physiochemical characteristics of the *in vivo* environment. Thus, cortisone, by reducing the inflammatory reaction, is likely to decrease the production of lactic acid at the site of a lesion. Hence, as pointed out by Dubos, it appears that susceptibility to infection is an expression of a reversible disturbance, probably biochemical in nature. In view of the above, Dubos has wisely shown that whereas the emphasis in the control of infectious diseases has been placed *on a direct attack on the microbial parasites, a new phase of germ theory may* well evolve, if it becomes possible to identify the metabolic factors and to design techniques for their control. Certainly, this will lead to more concern for the host, who, in the final analysis should receive the first consideration.

PATHWAYS OF DEVELOPMENT OF URINARY TRACT INFECTIONS

In general, there are three possible pathways, or mechanisms of development, of urinary tract infections: hematogenous, contiguous, and retrograde. Obviously, these various routes or pathways by which the organisms invade the urinary tract are very important, in that they serve to indicate the location of infectious reservoirs which must be considered in the light of ultimate treatment.

On November 17, 1891, Dr. William H. Welch[3] presented interesting facts pertaining to infection of the human body by the Bacillus coli. At that time, he demonstrated that lesions of the mucous membranes of the intestines opened the way for the invasion of the colon bacillus into the bloodstream and thence to various organs and parts of the body. He pointed out that it was not to be inferred that ulceration, or other lesions of the intestinal mucosae, are necessarily associated with the invasion of the colon bacillus in sufficient numbers to be demonstrable by ordinary methods, but often such invasion is a frequent result of the lesion. At this time, the concept of focal infection in relation to systemic disease is firmly established and represents one of the most important factors in the treatment of patients suffering with infection. Any localized infection is potentially a focus, from which bacteria, their toxins, or other dissoluted products may at any time spread via the contiguous tissues, bloodstream, and lymph channels to induce an infection in communicating or distant tissues or to sensitize them. It is unreasonable to expect, therefore, that the removal of focal infections will eliminate a well established disease process which is characterized by fibrosis or tissue necrosis. Nevertheless, it is important to search carefully in hopes of detecting a possible focus of infection. No doubt many potential or established foci of infection may and can be successfully eradicated with the use of the antimicrobial agents alone. For this reason, many unrecognized foci of infection are eradicated without their exact location or nature being known. In a recent survey of the incidence of pyelonephritis during the antibiotic era, a

[3] Welch, W. H.: Med. News of Phila., 59: 669-671, 1891.

significant decrease in the frequency of its occurrences in autopsies within recent years was revealed[4]

Since approximately ninety five per cent of urinary tract infections are associated with bacteriological incitants which are normally indigenous to the alimentary canal, a great deal of attention has been given to this area as a possible route of urinary contamination Evidence has been presented showing a definite correlation between the urinary and fecal flora which suggests that the feces probably represents a major source of resistant strains isolated in the urine after therapy Furthermore, studies dealing with diabetic females in particular stressed the importance of perineal hygienic measures as a precaution against reinfection of the urinary tract Likewise, actual pathologic changes in the urinary tract may result from complications of the colon, such as diverticulitis, extraperitoneal appendicitis, and regional enteritis In such instances, active therapeutic treatment is directed towards the bowel as the urinary complication will usually disappear after bowel surgery and regression is thereby anticipated in all but the very chronic cases, since the major bacteriologic process is not intrinsic in the urinary tract In view of the fact that infections of the urinary tract are encountered more often in the practice of medicine than any other group of diseases, with the possible exception of those involving the respiratory tract, we find that most of these cases are treated initially by the generalist No doubt many acute, uncomplicated cases are thus successfully treated Nevertheless, we are seeing an increasing number of urinary tract infections which have failed to respond to the now available forms of therapy It is this latter group, the so called therapeutic failures, that often reaches the urologist and represents a real challenge Let us therefore consider certain of the factors which lead to this situation

FACTORS PREDISPOSING TO THERAPEUTIC FAILURES IN URINARY TRACT INFECTIONS ERRORS IN DIAGNOSIS

In acute infections and under conditions where time and inadequate facilities preclude urine cultures, examination of stained urinary sediments can be quite helpful By this means, it is possible to determine in many cases whether one or more organisms are involved and at the same time to obtain some clue to the morphologic and possibly the generic identity of the organisms This information, coupled with a knowledge of the antibacterial spectra and pharmacologic behavior of the different antimicrobial agents, will permit institution of therapy This procedure constitutes the bare minimum upon which to base a rational therapy

However, recent studies by us cast doubt upon the reliability of a single urine specimen for culture as a basis for determining the causative agent or agents of a urinary tract infection[5] In a group of patients with urinary tract whereas some are essential to Man's survival. Fortunately, a number of the harmful bacteria have succumbed to the antimicrobial agents, some have survived because of their effective protective mechanisms against these drugs, and others which were initially stunned have developed new defenses and are back on the firing line. Furthermore, others which ordinarily are not injurious to Man, have become agitated and are now pathogenic to Man. Since these chemotherapeutic agents have no respect for members of the bacterial world, we find that in the process of successfully combating a disease state often bacteria, which are helpful to Man in his struggle for existence, are destroyed.

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[4] Kipnis, G P , Jackson, G G , Dallenboch, F W and Schoenberger, J A Arch Int Med , 95 445–450 1955

[5] Flippin, H F and Eisenberg G M Antimicrobial Therapy in Medical Practice Philadelphia F A Davis Co , 1955

For the most part, every known chemical substance can produce a toxic reaction in Man if the exposure is adequate, thus making the use of these chemotherapeutic drugs by Man a potential hazard. Each chemical agent has a nontoxic and a toxic dose, thereby making variable the factor of exposure. Furthermore, the severity of toxicity varies greatly with the method of administration, the degree and duration of the drugs used, and the condition of the patient. Unfortunately, the toxicity of chemical substances for use in Man cannot be determined conclusively on animals, although toxicity studies involving animals alone can give reasonable assurance that the drug may be tried in Man with some degree of safety. However, no criteria involving animals alone can prove toxicity or nontoxicity for Man, thus making necessary toxicity determinations by human experimentation.

As a result of the above factors, we are confronted today with certain serious and unsolved problems relating to the use of these antimicrobial agents—namely, an increasing number of drug-resistant organisms, infections caused by microorganisms usually regarded as nonpathogenic, which occur during antibiotic therapy that prove insensitive to the drug being employed, as well as the toxic reactions of these therapeutic agents.

DRUG-RESISTANT INFECTIONS

The widespread and indiscriminate use of the antimicrobial agents has resulted in an increased number of drug-resistant bacteria. This increased microbial resistance following exposure to an antibiotic not only holds for the antibiotic itself but also the possibility of the development of cross-resistance to other antibiotics exists. In considering this problem of drug-resistant infections, one must distinguish between the natural and the acquired resistance of microorganisms. Natural resistance or susceptibility to these agents varies widely among bacterial species, as well as among different strains of a given species. Acquired resistance for the most part results from continued exposure to subinhibitory concentrations of these drugs. The development of resistance to streptomycin often occurs within a period of a few days, whereas very few organisms become resistant to penicillin.

At this time there is considerable controversy as to whether resistant strains appear because a few organisms that were originally present were genetically resistant to the antibiotic and grew out in large numbers as the remainder were inhibited by the antibiotic; or, whether in the presence of an antibiotic, resistant mutants were allowed to survive and encouraged to proliferate Regardless of the mechanism, it would appear that the organisms which were originally present in small numbers, or which were implanted from outside sources in small numbers, overgrow the predominant organisms because the latter are susceptible to the antibiotic, while those which replace them are not

Hence, the problem of acquired drug resistance naturally raises the question as to whether it will ever be possible to find antimicrobial agents that will not induce resistance Certainly, a therapeutic agent possessing specific killing properties presumably has the capacity to interfere with some part of a function which is vital to living organisms but not vital to the host In both instances such a function or bypath must be more or less remote from the most fundamental features of life itself This immediately implies the possibility for bypassing the function and once this is realized, regardless of the manner of its occurrence, there will be resistance In other words, a substance incapable of inducing resistance would seem to have little chance for possessing antimicrobial activity

At this time, it appears that the problem of antibiotic-resistant bacteria is the greatest fear in the future with chronic infections of the respiratory tract and urinary tract, as these are usually mixed infections and are perpetuated by physiological and anatomical defects in the host In such instances, these drugs cannot do more than provide temporary help and hence should be reserved to *prepare the patient and carry him through the period necessary for the correction* of an anatomic or physiologic defect Thus, the best way to prevent the emergence of resistant strains is by the rapid termination of the infection and the optimum correction of anatomic defects

Furthermore, in view of the possibility of drug resistant organisms developing, it would appear that the use of antimicrobial agents may unfavorably affect the postoperative infective rate in clean surgery Not only is prophylaxis of doubtful efficacy, but at the same time it may mask and delay the appearance of wound infections It would seem, therefore, that important time and expense will be saved by the restriction of antibiotics to the early treatment of established infections in the few cases in which they do follow clean operations Along these same lines, it is well to point out that every effort be made to protect the patient from individuals harboring drug resistant bacteria No doubt the increasing incidence of drug-resistant staphylococci found in hospital practice is due to the fact that patients admitted with these organisms transmit the same to other patients or to hospital personnel, who, in turn, act as carriers Certainly isolation techniques alone are not sufficient and it seems practical that all surgeons and nurses wear masks and gloves while dressing wounds

SUPERINFECTIONS

Antimicrobial therapy, in addition to eliminating the causative organisms of the infection, produces a profound alteration in the composition of the bacterial population that normally inhabits certain tissues and organs The mechanism by which superinfection occurs during antimicrobial therapy is not clear

Normally, the body harbors many organisms which in small numbers are not pathogenic, relatively avirulent, and cause no symptoms. When the normal ecology or microbiological balance is disturbed by antimicrobial therapy, such organisms may increase in numbers and invasiveness and give rise to infections. Occasionally, infections with micro-organisms usually regarded as nonpathogenic will occur during antibiotic therapy and prove to be insensitive to the drug being employed. Such superinfections result from the dislocation of the normal bacterial flora of the sino-respiratory, gastrointestinal, and genitourinary tracts. Several mechanisms to explain these superinfections have been postulated: a) Administration of antibiotic results in virtual elimination of susceptible organisms, thus reducing the numbers competing for available food supply. The resistant organisms then vastly increase in numbers and overwhelm the host's resistance. b) Normal flora supplies certain nutritional requirements of the host. Disturbance in the normal flora results in a nutritional disturbance which modifies the integrity of the mucous membranes, thereby opening a portal of invasion to organisms which normally are unable to penetrate the healthy mucosa. c) Some antibiotics, like chlortetracycline, are suspected of directly stimulating growth and virulence of Candida albicans, with the ultimate production of candidiasis. In all probability, the mechanisms concerned involve alterations in both the host and the normal bacterial flora that follow the administration of an antibiotic. Such an opportune combination results in the appearance of a complicating infection during the course of a disease that appears to be responding favorably to chemotherapy. Hence, the importance of bacteriological studies to follow the changes in bacterial flora in various regions of the body in patients being treated for infectious diseases. For the most part, these micro-organisms attack the same organs which were involved in the primary disease, but as a rule, these organisms prove difficult to treat with the presently available drugs. It would seem, therefore, that there is a definite danger in using antimicrobial agents in diseases that are not treatable, since superinfection, which may be a very small risk in untreated infections, may thus become a serious threat. In addition, prophylactic therapy will not prevent secondary infections in many cases, thus it is doubtful whether it will reduce the incidence of superinfections in some diseases.

TOXIC REACTIONS

In evaluating the toxicity of drugs in Man, one not only considers the immediate side effects, but also the delayed reactions which may require years of observation. Certain of these side effects are toxic, some are allergic, and others are related to the biologic activities inherent in the chemotherapeutic substances themselves.

PENICILLIN

The chief untoward reactions to penicillin therapy fall into three principal groups: 1) local contact (skin, mucous membranes, and injection site); 2) dermatological allergy (urticarial, erythematous, and eczematoid); 3) systemic (serum sickness, anaphylactoid, cardiovascular, and renal). In addition, there have occurred certain specific phenomena associated with some particular disease being treated with penicillin, such as the Herxheimer reaction in syphilis and the development of a Loeffler's syndrome following aerosol penicillin in the treatment of some types of pulmonary disease. Furthermore, evidence is pointing towards penicillin's giving rise to a variety of disorders including agranulocytosis, periarteritis nodosa, the production of L E cells in the bone marrow, and others.

At the time that penicillin was first made available for general civilian use, it was not fully understood how many of the toxic reactions described were due to impurities in the penicillin preparations, or to the drug itself. Probably, the total incidence of penicillin reactions was decreased because of the increased purity of the drug and the introduction of procaine penicillin. However, the total number of reactions has increased steadily and today penicillin heads the list of medicinal agents in frequency, diversity, and severity of the sensitivities it produces. No doubt this is a result of the fact that the drug is used promiscuously and repeated administration of it to ever increasing numbers of people has resulted in their being conditioned to show various manifestations of hypersensitivity when exposed to subsequent penicillin therapy. Rarely does a patient experience a reaction after the first dose of penicillin, whereas the reactions become more frequent and more severe in individuals who have repeated doses. Some of the reactions occurring after the first dose are believed to be related to cross reactions with other fungi, particularly trichophytosis (athlete's foot). The more serious reactions, such as anaphylactic shock, occur *most often in patients with allergic histories, especially asthma. Although any* penicillin preparation and any mode of administration can cause a reaction, it appears that oral penicillin is the least likely, parenteral preparations are next in frequency, and topical penicillin the most likely to cause reactions. Reports of acute anaphylactoid reactions due to penicillin are being published with increasing frequency, with most of the severe cases following the administration of procaine penicillin. This may be due to a greater amount of sensitizing substance that is present longer or to the possible synergistic effect when two substances are injected simultaneously.

In spite of the foregoing, penicillin remains the least toxic of the currently available antimicrobial agents. Its well established therapeutic value and relatively lower cost combine to establish it as the most popular drug. Hence, every effort should be made to minimize the reactions following its administration. A history of previous penicillin toxicity should, in most cases, contraindicate the use of penicillin and manifest the desirability of administering another antibiotic, if possible. However, many patients can tolerate penicillin, even after a previous allergic reaction, and, in such conditions as subacute bacterial endocarditis in which penicillin is strongly indicated, one may proceed with caution. When reactions do occur and are not too severe, treatment can usually be continued with the aid of antiallergic remedies. Obviously, the more serious reactions demand discontinuance of the drug. Such reactions as anaphylactoid shock and exfoliative dermatitis demand prompt attention and treatment with supportive measures, epinephrine, antihistaminics, and ACTH

The advisability of using a penicillin product in which an antihistaminic agent is included can be questioned, in that one is adding another potentially toxic agent. Where possible, oral penicillin should be used in preference to the parenteral route. Intramuscular injections must be given with caution, as it has been implied that some of the severe, or fatal, reactions are the result of the accidental intravenous injection of procaine penicillin. Topical application in the form of troches, toothpaste, aerosol, ointments, and dusting powders is of doubtful value in most instances and should be discouraged.

Some investigators rely on skin testing as a guide in determining possible penicillin sensitivity, but as yet there seems no complete agreement as to the value and significance of skin test results, with the possible exception of the immediate whealing reaction on cutaneous or intracutaneous testing as regards the development of an anaphylactoid reaction.

Efforts to desensitize patients who have experienced penicillin reactions have been considered successful in the hands of some experienced workers. This procedure may be tried, especially when the patient's occupation, e.g., nursing, necessitates exposure to the drug, or in conditions where penicillin is urgently needed. If the sensitivity reaction has been severe, an initial dose of 2 units of aqueous penicillin G is given intramuscularly, whereas other cases are given 50 units every 3 hours the first 24 hours, 100 units every 3 hours the second 48 hours, with the dose being doubled each 24 hours until the patient can tolerate 200,000 units.

TETRACYCLINE

Chlortetracycline, oxytetracycline, and tetracycline frequently give rise to gastrointestinal and genitourinary disorders (nausea, vomiting, diarrhea, stomatitis, vaginitis, and proctitis). While these are not usually serious, they do cause considerable inconvenience and at times become quite severe. In our experience to date, chlortetracycline appears to be the most offensive in this manner. It is felt that these untoward reactions are due, at least in part, to alteration in bacterial flora leading to a vitamin B deficiency. There is evidence to support the view that chlortetracycline stimulates the growth of some types of fungi, notably Candida albicans and that these two factors combine to produce a moniliasis. When these drugs are used for periods exceeding 7 days, the patient should receive buttermilk, vitamin B complex, and B_{12} orally; if toxicity develops, the drug should be discontinued, if possible, and injections of crude liver, or B_{12} given daily. More recently, nystatin has been introduced as an agent for the prevention and management of gastrointestinal moniliasis.[7] Nystatin is available as 500,000 unit tablets to be given 3 times a day and is stated to be compatible with all the present orally administered antibiotics.

STREPTOMYCIN (DIHYDROSTREPTOMYCIN)

In general, the severity of toxicity from both streptomycin and dihydrostreptomycin is dependent upon the duration of therapy, total dose employed, and degree of renal impairment, the principal toxic effect being damage to the eighth nerve and vestibular apparatus While this is particularly true of streptomycin, there seems to be a lesser tendency of dihydrostreptomycin to affect the vestibular apparatus However, damage to the auditory branch of the eighth nerve with hearing loss may occur Since patients are able to compensate for damage to the vestibular branch, but not able to compensate for auditory damage, it is obvious that dihydrostreptomycin is less desirable, especially for long-term therapy, as is necessary in tuberculosis, than is streptomycin Occasionally, dihydrostreptomycin is useful in patients who are allergic to streptomycin as sometimes allergies do not develop in patients receiving this drug, whereas were they receiving streptomycin, allergies would develop The recent practice of employing mixtures of streptomycin and dihydrostreptomycin has markedly reduced this toxic effect Either of these compounds may give rise to a variety of less severe reactions, including the sensitivity reactions encountered with penicillin Certainly, special precautions are indicated in patients with impaired renal function who receive either streptomycin or dihydrostreptomycin

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CHLORAMPHENICOL

Chloramphenicol gives rise to the same toxic reactions as the tetracycline group, although one difference does exist, in that chloramphenicol exerts at times a toxic effect upon the hemopoietic system

ERYTHROMYCIN

Erythromycin appears to be of relatively low toxicity and the only undesirable effect noted in many patients treated with this drug has been an occasional gastrointestinal upset with high dosage It does not appear to have as adverse an effect on the ecology of the gastrointestinal flora as do the tetracyclines, some of the symptoms of the antibiogenic syndrome are thus avoided

POLYMYXIN

Although polymyxin B sulfate is an agent of considerable toxicity (renal and central nervous system), its unique effectiveness in infections due to Pseudomonas aeruginosa has justified its introduction into clinical practice This antibiotic should be employed parenterally only in hospitalized patients, since careful observation for renal damage is essential to its safe use

BACITRACIN

Since the parenteral administration of bacitracin is often followed by kidney damage, and only a small amount is absorbed when given by mouth, this drug finds its chief usefulness as a topical or oral medicament

NEOMYCIN

When administered systemically, neomycin may cause slight to severe deafness as well as transient renal irritation Since this drug is not absorbed into the circulating bloodstream from the gastrointestinal tract or skin, it has found its chief usefulness in preoperative preparation for intestinal surgery and as a topical medicament; although in selected cases, especially in Proteus and Pseudomonas infections, it may be administered intramuscularly for short periods of time.

ISONIAZID

The administration of isoniazid may be followed by a variety of untoward reactions, the severity of which depends on the dosage, length of administration, renal function, and personality stability. Such symptoms as increased reflexes, headache, muscular twitchings, peripheral neuropathy, euphoria, excitability, constipation, vertigo, dryness of mouth, and visual difficulties, are the principal toxic side-effects encountered. Cessation, or decrease, in therapy is dependent upon the type and severity of the reaction. Recently, the use of pyridoxine hydrochloride has been shown to be effective in relieving pain in cases with peripheral neuropathy.

NITROFURANTOIN

Nitrofurantoin (furadantin) has been well tolerated when given orally in daily dosage of 5 to 8 mg./kg. of body weight, in four divided doses, with meals and with a bedtime snack. Larger doses result in nausea and vomiting. The drug is tolerated without reaction even in patients known to be sensitive to the related compound, furacin.

NYSTATIN

Nystatin (mycostatin), derived from cultures of Streptomyces noursei, has been shown to inhibit or kill many species of fungi and yeasts. After oral administration, this antibiotic is poorly absorbed. Thus far, it appears to be virtually nontoxic following oral administration.

SULFONAMIDES

Despite the advent of penicillin and the other antibiotics, the sulfonamides are still being employed, especially in the treatment of urinary tract infections. In discussing the untoward reactions associated with their use, it is well to point out several factors which tend to influence their incidence and severity. The length of time that the drugs are administered and the total dose employed are probably the most important factors. Children seem to tolerate these drugs better than the aged; those with good nutrition and normal renal function better than the poorly nourished and those having kidney damage.

A variety of untoward reactions may follow the administration of the sulfonamides, some of which are mild, while others may be severe, or even fatal. Whereas most of these complications are seen during the administration of the drug, there are some, such as periarteritis nodosa, which become manifest at a later date. The most common toxic reactions are those of nausea, vomiting, fever, dermatitis, anemia, neutropenia, agranulocytosis, psychoses, and those referable to the urinary tract. This latter group may be manifested by hematuria, oliguria, or anuria and are most frequently encountered following the sulfapyrimidines. In this connection, the belief is widely held that administration of sufficient fluid to insure a high urinary output is enough to prevent crystalluria, which is responsible for most cases of urinary toxicity Nevertheless, high volumes of urine will not forestall precipitation of sulfapyrimidines, however, chemical and clinical studies of these compounds have demonstrated that the total amount of sulfonamide which can be held in solution in urine is substantially increased when two or more of these substances are administered simultaneously and that this is accomplished without sacrificing therapeutic activity Thus, it is possible to lessen the hazards of urinary tract complications due to sulfonamide crystals or calculi Hence, the rationale for the combination of sulfadiazine, sulfamerazine, and sulfamethazine However, it is still important when using the sulfapyrimidines to maintain a urinary output of at least 1200 cc daily

PROPHYLACTIC USE OF ANTIMICROBIAL AGENTS

In addition to their proven therapeutic value, the evidence is sufficiently abundant to say that these drugs are of value when employed prophylactically in certain specific instances ranging from the protection of the unborn to the prevention of complicating infections in the closing hours of life No doubt many types of infections have been avoided by the judicious use of the antimicrobial agents, but they have also been employed illogically, which has added to their indiscriminate use

COMMENT

Certainly, the art of water casting has changed tremendously since the Jerusalem Code of 1060 Likewise, we have witnessed significant advances in the management of urinary tract infections, although there remain many unsolved problems These recent prodigious advances in the field of anti infective agents exert a profound influence on the practice of urology, in that it has become possible to effect dramatic cures in a large percentage of patients suffering from infections previously dreaded, as well as to prevent infections which formerly proved disastrous However, just as each new discovery in medicine increases our knowledge and opens up new avenues of approach, it simultaneously imposes new challenges and increases our ignorance In view of the ability of these drugs to sensitize individuals, we may see in the future more severe reactions following their use Likewise, more micro organisms may develop resistance to these drugs and, with the ultimate dislocation of the normal bacterial flora of the body, more diseases which heretofore were not harmful may result Certainly, the danger signals have been hoisted and until such time as an ideal antimicrobial agent is developed, the physician should limit the use of these life saving agents to infections in which their therapeutic effectiveness has been demonstrated and to refrain from employing them prophylactically except when the complication to be avoided is a serious one and one which occurs frequently in the absence of precautions Furthermore, in spite of the proven therapeutic and prophylactic value of the antimicrobial agents, they are not to be used to the exclusion or neglect of other established forms of therapy Looking into the future, we may find that these antimicrobial agents will prove to be insidious purveyors of disease, in that Nature brooks interference badly and often defeats Man before he knows of his undoing

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THE ANTIBODY (HEMAGGLUTININ) RESPONSE OF PATIENTS WITH INFECTIONS OF THE URINARY TRACT

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Diagnosis of specific infectious diseases may be accomplished in the laboratory by isolation of the causative micro-organism or by demonstration of an increase in the titer of antibodies against the etiological agent. The latter method has been used infrequently and without particular success in patients with urinary tract infections, either because these patients do not respond with the formation of antibodies or because the available methods are not sensitive enough for their demonstration. Recent evidence suggests that red blood cells modified by certain bacterial antigens are more sensitive tools for the detection of bacterial antibodies than the antigens used alone in agglutination and similar serological tests. This indirect bacterial hemagglutination method (or its hemolytic modification) has been utilized for the demonstration of antibodies against components or products of several bacterial species.[1-12] The potentialities of this test in infections of the urinary tract appeared worthy of exploration. The present paper embodies the results of such an investigation and indicates that the hemagglutination test is distinctly superior to the hitherto available methods. Thus a number of problems related to acute and chronic bacterial infections of the urinary tract

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may now be studied, these include the relationship of the presence of antibodies (bacterial hemagglutinins) to the course of the disease, the development of antibodies in patients with malignancy or following radiation therapy as compared to controls, and the antibody response in patients with active tissue infection as compared to patients with asymptomatic bacilluria This report, then, presents the basic data needed for such a long range investigative program

MATERIALS AND METHODS

Subjects Adult patients with suspected or established urinary tract infection were selected for this investigation Patients were admitted to the Institute for diagnosis and therapy of malignancy Detailed clinical data were recorded (history, significant physical findings, treatment, and results of any special examinations, such as cystoscopy, excretory urography, retrograde pyelography, or interdepartmental consultations) Blood and urine were obtained from out-patients approximately every two weeks and from in-patients at weekly intervals as follows venipuncture specimens were drawn for hematologic and immunologic studies, urine samples for routine analysis and culture were collected in a sterile container, by catheterization in the female and by saving the second of two freshly voided specimens after antiseptic cleansing of the glans penis in the male

Bacteriological examination of urine Urine specimens were procured aseptically and forwarded to the Laboratory of Bacteriology as soon as feasible For a quantitative estimation of the number of nonfastidious bacteria, 1 ml of the urine specimen was mixed with 15 ml of liquefied and appropriately cooled brain veal agar, the mixture was poured into a sterile Petri dish and the number of bacterial colonies was determined after incubation at 37C for 24 to 48 hours Sediment of the urine sample was seeded on blood and Endo agar as well as into infusion broth In addition, a microscopic examination was performed on the urine sediment Bacteria isolated were identified by means of the usual methods Sensitivity tests, using the disc method, were interpreted qualitatively only

Preparation of antigens Aerobic, gram negative, nonfastidious bacilli isolated from the urine of patients were grown on brain veal agar in Kolle flasks for 24 hours at 37C The suspension was harvested in 25 ml of physiological saline and heated for 2½ hours in boiling water One part of 95 per cent ethyl alcohol was added to 9 parts of the antigen

Bacterial agglutination test Serial dilutions of patients' sera (volume 0 2 ml) were mixed with an equal volume of the above bacterial suspension, and the mixtures were kept in the water bath at 50C for 18 hours Resulting agglutination was read grossly

Bacterial hemagglutination test The methods employed were those described previously by Neter and associates[4 9] Briefly, red blood cells of man (blood group O) were washed three times and then mixed with a 1 10 dilution of the above bacterial antigen The mixtures were kept for 30 minutes in the water bath at 37C and washed three times This treatment results in the adsorption of bacterial antigen on the erythrocytes These modified red blood cells were then used as tools for the demonstration of homologous bacterial antibodies. To this end, patients' sera (volume 0.2 ml.) in serial dilution were mixed with equal amounts of modified red blood cells. The mixtures were incubated in the water bath at 37C for 30 minutes. Agglutination of the red blood cells was noted grossly both before and after centrifugalization at approximately 1500 r.p.m. for one minute. Marked agglutination results in the clumping of all red blood cells into a single clump, in contrast to hemagglutination caused by viruses, which is recognized on the basis of the pattern of sedimentation of erythrocytes. Lesser degrees of bacterial hemagglutination can be gauged without difficulty. Appropriate controls were included.

Hemagglutinin-absorption test. In order to demonstrate the specificity of the hemagglutination test and to differentiate among antibodies reacting with different serological groups or types of single bacterial species, the hemagglutinin-absorption test was carried out as follows: suitable dilutions of the patients' sera (volume 0.2 ml.) were mixed with serial dilutions of the respective bacterial antigen (volume 0.2 ml.); the mixtures were incubated for 30 minutes at 37C; modified red blood cells were then added and the hemagglutination test performed and read as described above.

RESULTS

Comparison of sensitivity of hemagglutination and agglutination methods. The first part of this study was devoted to a comparative evaluation of the sensitivity of the bacterial agglutination and hemagglutination methods, utilizing sera from patients with urinary tract infection and the homologous bacterial antigens. The results obtained indicate that the latter method was far more sensitive than the former. A representative example is presented in table 1:

G. J., RPMI No. 79986. A 81-year-old white man was first seen on February 8, 1954 for investigation of painless gross hematuria of 2 months' duration. Cystoscopic biopsy revealed transitional cell carcinoma of the urinary bladder. Urine studies on admission revealed microscopic hematuria and pyuria. Following transurethral resection of a solitary bladder tumor, the patient complained of frequency, urgency, burning, and nocturia. Urine analysis on April 19 continued to show hematopyuria. Urine culture revealed innumerable colonies of

TABLE 1. *Comparison of sensitivity of Paracolobactrum hemagglutination and agglutination methods*

Dilutions of Patient's Serum	Agglutination of	
	Modified red blood cells	Bacteria
1/10	4	1
1/20	4	—
1/40	4	—
1/80	3	—
1/160	1	—
1/320	—	—
0	—	—

1 to 4 = progressively increasing degrees of agglutination or hemagglutination.
— = no agglutination or hemagglutination.

Paracolobactrum When subsequent urine cultures on May 17 and July 14 showed innumerable colonies of the same organisms, hemagglutination study was begun Therapy with nitrofurantoin gave an excellent clinical response and urine culture was negative on September 10

The data recorded in table 1 show that the serum of this patient caused hemagglutination in a dilution of up to 1 160 and bacterial agglutination in a dilution of only 1 10 This result indicates the greater sensitivity of the bacterial hemagglutination method over the conventional bacterial agglutination test Similar data, presented below, were obtained in other patients of the present series, with a variety of bacterial species, and without exception the hemagglutinin titer was substantially higher than the agglutin titer

Appearance of bacterial hemagglutinins in serum of patients with infection of the urinary tract If these bacterial hemagglutinins represent response of the patient to the micro organism causing the urinary tract infection, one should be able to demonstrate their appearance during the early course of the disease This is illustrated in the following case of Pseudomonas aeruginosa infection

J G, RPMI No 80648 A 66 year old white man was first seen at the Roswell Park Memorial Institute on April 28, 1954 He complained of persistent burning on urination Previous treatment for bladder tumor had been given elsewhere, consisting, in essence, of transurethral fulguration (1951), segmental vesical resection (1953), and transurethral resection (March 26, 1954) Pathological examination of the tumor resected in March 1954 showed carcinoma, grade 2 Except for nodularity at the region of the bladder base, physical examination on April 28 revealed no significant abnormalities Excretory urography indicated satisfactory function and normal structure of the upper urinary tracts Cystoscopic biopsies (April 28 and August 20) in suspicious areas revealed only inflammatory changes Since August 13, urine cultures persistently grew innumerable colonies of Pseudomonas aeruginosa, and the symptoms persisted despite treatment with sulfisoxazole, nitrofurantoin, and sulfamethylthiodiazole (thiosulfil)

The data recorded in table 2 indicate that hemagglutinins developed in this patient between August 13 and August 20 The hemaggultinin titer rose from less than 1 10 to 1 640 The antibody titer remained at significant levels for the next 2 months

An example of a rising hemagglutinin titer is documented in a patient suffering from Escherichia coli infection of the urinary tract

R G, RPMI No 81666 A 43-year old white woman, first seen on August

TABLE 2 *Appearance of bacterial hemagglutinins in serum of a patient with Pseudomonas aeruginosa infection of the urinary tract*

Date	Bacterial Hemagglutinin Titer
8/13/54	Less than 1 10
8/20/54	1 640
8/27/54	1 320
9/13/54	1 160
10/15/54	1 320

TABLE 3. *Increasing titers of bacterial hemagglutinins in serum of patient with Escherichia coli infection of the urinary tract*

Date	Bacterial Hemagglutinin Titer
8/30/54	1:80
9/27/54	1:1280
10/11/54	1:1280

TABLE 4. *Bacterial hemagglutinins in serum of patient with Aerobacter aerogenes infection of the urinary tract and in random patients' sera*

Patients	A. aerogenes Hemagglutinin Titer
H.A.	1:2560
Random cases	
1	1:10
2	Less than 1:10
3	Less than 1:10
4	Less than 1:10
5	Less than 1:10
6	Less than 1:10
7	Less than 1:10
8	Less than 1:10
9	Less than 1:10

24, complained of painful gross hematuria of 2 weeks' duration. Right costovertebral angle tenderness was present on initial examination. Cystoscopy revealed vesical mucosal changes consistent with mild cystourethritis, and urine cultures on August 30 and September 27 revealed the presence of E. coli. Excretory urography demonstrated normal structure and function of the upper urinary tracts. Periodic urethral dilatation was performed, and the patient's urinary symptoms subsided promptly. Subsequent urine cultures on October 11 and November 15 were sterile.

The data recorded in table 3 show that the titer of bacterial hemagglutinins rose from 1:80 on August 30, to 1:1,280 on September 27, 1954. This rise in hemagglutinin titer occurred within 2 weeks after the appearance of symptoms of infection. The data, therefore, suggest that the increase in hemagglutinins represents a specific antibody response to the E. coli infection.

The presence of bacterial hemagglutinins in random human sera. If the presence of bacterial hemagglutinins in the sera of the above patients represents specific antibody response to the infection, one should then postulate that random human sera obtained from individuals without infection of the urinary tract do not have these hemagglutinins in corresponding titers. To elucidate this point, the titer of hemagglutinins against Aerobacter aerogenes in the serum of a patient (H. A.) with Aerobacter aerogenes infection of the urinary tract was compared with the titer of antibodies in sera obtained from nine random cases. The results of this study are summarized in table 4.

The data recorded in table 4 show that the hemagglutinin titer of the serum of the patient against his own strain was 1:2,560. In contrast, the nine sera obtained from random cases did not have hemagglutinins against this microorganism in a titer higher than 1:10. Similar observations were made with other sera and bacterial antigens and revealed that titers of bacterial hemagglutinins against heterologous bacterial antigens rarely were present in titers of 1:160 or higher.

The type- or group specific bacterial hemagglutinin response of patients with infection of the urinary tract. Many of the bacterial species (Escherichia, Aerobacter, Paracolobactrum and others) responsible for urinary tract infection of human beings are known to be comprised of several serologically different groups. For this reason, study was made to determine if the hemagglutinin response of patients with infection of the urinary tract is species- or group-specific. The hemagglutinin response of a patient with a mixed infection of the urinary tract due to Escherichia coli and A. aerogenes was studied simultaneously with strains isolated from this and other patients.

M. H., RPMI No. 71698. A 55-year old white woman began to have urinary frequency and burning in June 1954. In 1951 and again in 1952, she had extensive pelvic surgery for primary adenocarcinomas of the uterus and of the left ovary. X-ray therapy had been given also in 1951. Since June 1953, she had been receiving local bladder instillations of silver nitrate solution for a late radiation reaction. Urine cultures during the past year revealed the presence, singly or in combination, of Staphylococcus aureus hemolyticus, Proteus ammoniae, Aerobacter aerogenes, Streptococcus non-hemolyticus, and Escherichia coli, despite periodic systemic treatment with penicillin, sulfisoxazole, and chloramphenicol. The urine culture on September 10 revealed A. aerogenes and E. coli. After a series of urethral dilatations failed to improve the patient, nitrofurantoin was administered systemically with sudden symptomatic improvement. Excretory urography, however, revealed bilateral hydronephrosis, and her urine cultures remained positive.

The data recorded in table 5 show that the patient's serum obtained on September 10, October 1 and October 22 contained hemagglutinins against both of her strains of E. coli and A. aerogenes. In contrast, the same sera did not cause hemagglutination of red blood cells which were modified by heterologous strains of E. coli and A. aerogenes obtained from other patients. Furthermore, the sera of the latter patients were found to agglutinate red cells which were modified with the homologous antigens. These findings indicate that the antibody

TABLE 5. *Type (group) specific Escherichia coli and Aerobacter aerogenes hemagglutinin response of patient with infection of the urinary tract*

Patient's Serum (Date)	E. coli		A. aerogenes	
	Homologous	Heterologous	Homologous	Heterologous
	Hemagglutinin titers			
9/10/54	1:640	Less than 1:10	1:640	Less than 1:10
10/1/54	1:640	Less than 1:10	1:80	Less than 1:10
10/22/54	1:320	Less than 1:10	1:80	Less than 1:10

TABLE 6. *Hemagglutinin-absorption test*

Absorbing Antigen	Result of E. coli Hemagglutination Test
E. coli, homologous	−
E. coli, heterologous	+
A. aerogenes, homologous	+
A. aerogenes, heterologous	+

+ = hemagglutination.
− = no hemagglutination.

response, as measured by the bacterial hemagglutination test, against E. coli and A. aerogenes, is a group-specific rather than species-specific. Such a result is to be expected, since these bacterial species are comprised of numerous serogroups and serotypes.

Hemagglutinin-absorption test. If the observed agglutination of red blood cells modified by various bacterial antigens is due to the actual presence of bacterial antibodies in the sera of these patients, the removal of these antibodies by means of homologous bacterial antigens should be possible. This was accomplished, as illustrated in the data presented in table 6. In this experiment, the serum of patient M. H. (see table 5), before and after absorption with several bacterial antigens, was tested with red blood cells modified by E. coli antigen prepared from the patient's own strain.

Table 6 indicates that the E. coli antibodies were removed from the serum only by the homologous strain of E. coli and not by a different strain (group) of the same bacterial species. Moreover, Aerobacter aerogenes, obtained either from the patient or elsewhere, failed to absorb the E. coli antibodies. These data again reveal the specificity of the hemagglutination test and clearly show differences between several strains of E. coli and between E. coli and A. aerogenes. The results suggest strongly that the factor in the serum responsible for hemagglutination is indeed an antibody.

Persistence of bacterial hemagglutinins in the sera of a patient with infection of the urinary tract. How long hemagglutinins persist in these patients was studied next. An example of the persistence of bacterial hemagglutinins in high titer is illustrated in the following case:

S. S., RPMI No. 25447. An 81-year-old white man has been under continuous observation since 1936, when a squamous cell carcinoma of his bladder was diagnosed by biopsy and treated by radium pack emanation. Since that time he has complained of urinary hesitancy, burning, and nocturia. Urethral instrumentation has been exceedingly difficult. Endoscopically, depressed bladder capacity and a contracted vesical neck have been observed. X-ray studies revealed a poorly functioning right hydronephrosis. Since 1948, pyuria has been present and urine cultures have grown various combinations of Staphylococcus, Streptococcus, Proteus, E. coli, and Pseudomonas. From August 18, 1954 until December 1, 1954, ten consecutive pure cultures of Pseudomonas aeruginosa were obtained, despite intensive administration of many antibiotic and chemotherapeutic agents.

TABLE 7. *Homologous bacterial hemagglutinins in titers of 1:160 and above in sera of patients with urinary tract infection*

Bacterial Species	Number of Patients*	
	Positive	Negative
Escherichia coli	2	2
Aerobacter aerogenes	5	2
Paracolobactrum	6	5
Pseudomonas	5	7
Proteus.	2	3
Alcaligenes	0	1
Total	20	20

* Includes cases with multiple infection

Eight serum specimens obtained from this patient between August 18, 1954 and November 18, 1954 all contained homologous bacterial hemagglutinins in high titer (1:6,400). In this particular patient, the infection persisted. Data are not available in the present study regarding the persistence of bacterial hemagglutination following recovery from the infection.

Demonstration of bacterial hemagglutinins in significant titers in the sera of patients with infection of the urinary tract. The data obtained in these bacterial hemagglutination studies on twenty patients with infection of the urinary tract are summarized in table 7. Six different bacterial species were encountered, namely, E. coli, A. aerogenes, Paracolobactrum, Pseudomonas, Proteus, and Alcaligenes. On the basis of studies of patients' sera and heterologous antigens it appears that a titer of bacterial hemagglutinins of 1:160 and above is uncommonly found. For this reason, sera containing hemagglutinins in titers of 1:80 or less were considered as negative and sera with titers of 1:160 and above as positive. The sera of 20 patients were tested with antigens prepared from the patients' own strains. Since the urine from some of the patients harbored more than one type of micro-organism, their sera were studied with more than one bacterial antigen In all, 40 antigens were available. Significant titers were detected with twenty, or 50 per cent, of these antigens. Had serum specimens taken one to three weeks after infection been available in all cases, additional positive results might have been obtained. Table 7, furthermore indicates that, with the exception of a single strain of Alcaligenes, antibodies to all groups of micro-organisms were found.

DISCUSSION

This investigation was undertaken in order to find a practical method for the determination of antibodies which will be more sensitive than the conventional and hitherto available bacterial agglutination test in the study of patients with infections of the urinary tract. The data obtained in this study indicate that the hemagglutination method offers this advantage. The bacterial hemagglutination test was far more sensitive than the conventional bacterial agglutination method, and antibodies were demonstrated in patients with infection due to a variety of gram-negative bacilli, including E. coli, A. aerogenes, Proteus, Pseudomonas, and Paracolobactrum. In random human sera, bacterial hemagglutinins were found only in low titer. That the active principle in the serum is indeed an antibody is substantiated by the results of hemagglutinin-absorption tests. Of course, many more patients will have to be investigated by means of this hemagglutination test before conclusions can be drawn as to the frequency with which these individuals respond with the formation of specific bacterial hemagglutinins. The data obtained warrant further investigations in this direction and may eventually aid in the solution of many problems. For example, with presence of more than one bacterial species in the same urine sample, differentiation conceivably may be made between the infecting and the contaminating micro-organism by determining the hemagglutinin response of the patient. By this information, one may be guided in the selection of the appropriate antibiotic. The hemagglutination and hemagglutinin-absorption methods also promise to be of value to distinguish between relapse of an old infection and a new infection with an antigenically different micro-organism, even though both may belong to the same bacterial species. Finally, it is now possible to compare the antibody response of patients suffering from both urinary tract infection and malignancy with that of similar individuals with urinary tract infection only, and to assess the effect, if any, of x-radiation on the hemagglutinin response of such patients.

SUMMARY

A study was undertaken on the antibody response of 20 patients with infection of the urinary tract, utilizing the new bacterial hemagglutination method and the conventional bacterial agglutination test.

Hemagglutinins were demonstrated against a variety of bacterial species, including E. coli, A. aerogenes, Proteus, Pseudomonas, and Paracolobactrum.

The hemagglutinin titers without exception exceeded those obtained with the bacterial agglutination test.

The appearance of these hemagglutinins and a significant increase in their titer were demonstrated within a few weeks of the onset of evidence of infection in some of these cases.

In other cases, with continuation of the infection, hemagglutinin titers remained at high levels for a period up to three months.

In multiple infection, hemagglutinins against more than one bacterial species were demonstrated.

The specificity of these antibodies was demonstrated by the use of heterologous antigens as well as by means of the hemagglutinin-absorption method.

The data obtained in this study warrant more extensive investigation of the potential usefulness of the bacterial hemagglutination test in patients with infection of the urinary tract.

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USE OF BAG URETERAL CATHETERS FOR NEPHROGRAMS OBSTRUCTIVE NEPHROGRAMS

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Diagnostic and therapeutic technique in urology has reached a stage where emphasis is now being placed on the necessity for early diagnosis to further improve therapeutic results The foundation for early diagnosis in urology is still the use of cystourethroscopy and urography combined with a thorough history and physical examination However, when a search is made for suspected disease in the kidneys by excretory or retrograde pyelograms, there is dependence on changes that will distort or displace the collecting system An early lesion in the parenchyma that does not involve the calyces or pelvis may well be overlooked When such involvement occurs, it all too often heralds advanced pathological changes that may not be amenable to curative treatment The urologist is occasionally faced with the problem of bleeding from the upper urinary tract, the cause of which cannot be ascertained by exhaustive urologic survey—the so-called "essential hematuria" cases Surgical exploration of the kidney often is a synonym for nephrectomy in these cases, as actual exploration can only be done in limited manner Expectant followup in such a case may mean waiting for development of an advanced lesion For diagnostic problems that arise where good delineation of the renal parenchyma would be of value, we must rely on nephrography The term "nephrogram" or "nephrography" is not being used in this instance to include visualization of the renal outline as seen on the plain film or after retroperitoneal air insufflation

This paper is presented to emphasize the potential value of nephrography in the diagnosis of renal parenchymal lesions, and our experience with the technique of obstructing the ureter by bag catheters to obtain nephrograms

BACKGROUND

It has long been known that intensification of the renal shadow can occur with intravenous urography in the face of acute ureteral obstruction This "secondary x-ray sign" of ureteral obstruction was pointed out by Wesson and Fulmer as early as 1932 Hellmer was the first author to emphasize the possible value of nephrography as an aid in the diagnosis of renal parenchymal disease He showed two illustrations of nephrograms with areas of decreased density which proved to be a renal tumor and a cyst These nephrograms resulted from accidental ureteral obstruction or external compression, and not from artificially induced ureteral obstruction Leighton's work proved the potential value of nephrography as a tool for early diagnosis of kidney disease He produced small infarcts in dog kidneys using an electric current to devitalize small segments of tissue The ureters were then ligated and intravenous urography carried out Leighton

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showed several nephrograms in which small devitalized areas in these kidneys were clearly demarcated as radiolucent zones.

With the techniques now available, nephrograms can be produced on the basis of two different principles. One of these is by concentration of contrast media in the vascular network of the kidneys. The procedures of aortography and rapid intravenous injection of dye as advocated by Rose et al. utilize this principle. The production of nephrograms by this method is dependent on the rapid injection of dye followed by prompt x-ray exposure, as sufficient dye concentration to show the renal parenchyma adequately for diagnostic purposes will only be present for a very short time. The second principle is based on the concentration of contrast media in the tubules of the kidney. In the presence of acute ureteral obstruction, the intrarenal pressure may reach a level at which glomerular filtration is suppressed. This suppression of glomerular filtration is apparently not associated with cessation of tubular function. Therefore, iodides may be secreted into the renal tubules where they will remain, creating a diffuse accentuation of the kidney on roentgen examination.

Hickel (in the French literature) was the first to try to produce nephrograms by a method of internal obstruction of the ureter. He inserted ureteral catheters and connected them to a fluid reservoir to produce constant hydrostatic pressure. Weens and Florence were the first to publish an account of a simple method for artificial obstruction of the ureter to produce nephrograms. They utilized the Dourmashkin bag ureteral catheter. After insertion of the catheter into the abdominal segment of the ureter, the bag was inflated with mercury to obstruct the ureter and 35 per cent diodrast was given intravenously. Leighton, working independently, also reported use of internal ureteral obstruction for nephrography. He used a bag ureteral catheter which was constructed by Wild. This catheter was a modification of the Dourmashkin catheter and allowed easier introduction into the ureter. Illustrations shown by these authors showed nephrograms of good quality, both of normal renal parenchyma and parenchymal lesions.

METHOD AND MATERIALS

Many of the special techniques for diagnosis in medicine today are complicated, requiring special materials, training and personnel, and in some cases, carry considerable risk to the patient. Although they may be extremely valuable as an aid in a certain diagnostic problem, they may not be adaptable to everyday practice, and, hence, not used as often as they should be. The procedure of ureteral obstruction by bag ureteral catheters to obtain nephrograms requires no complicated equipment and can be carried out without undue time and effort on the part of the urologist or patient.

The bag catheter. The ureteral catheter used for this procedure is a modification of the Dourmashkin bag catheter and was developed by Leighton and Wild. It was easily made up at our clinic and required no special materials. A 5F radiopaque ureteral catheter with filiform tip is used. A thin latex sheath approximately 1.5 cm. in length is fitted over the hole near the tip of the catheter and secured to the catheter at either end with fine black silk, using a whip knot.

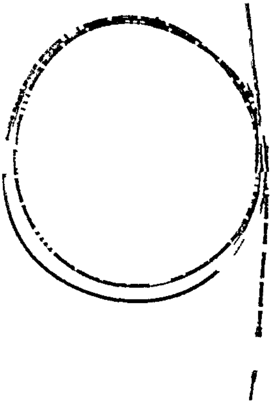

Fig 1 Bag catheter ready for use

Since these materials fit snugly, there is no appreciable increase in the diameter of the catheter (fig 1) The bag is inflated by injection through the lumen of the catheter

Other materials The only additional equipment required is that which would be used in routine retrograde and intravenous pyelography This includes one or two Luer Lok syringes fitted with 20 gauge needles, one or two hemostats, medicine glass containing a small amount of radiopaque dye, equipment for intravenous dye injection, and the cystoscope We use the 24F Brown Buerger cystoscope with convex sheath This size cystoscope will easily accommodate two bag catheters if both ureters are to be catheterized It is advisable to insert the bag catheters into the catheterizing element in a retrograde manner so as to avoid tearing the delicate latex sheath, which may occur if they are pushed through the rubber tips

Preparation of the patient This aspect is placed under a separate sub heading to emphasize the importance of having the patient well prepared prior to this procedure Fecal and gas content in the bowel makes for difficult interpretation of any urogram, but particularly so in nephrography Overlying gas shadows etc will completely eliminate the possibility of locating a small radiolucent zone in the kidney parenchyma representing an early lesion Figure 2 illustrates this showing an obstructive nephrogram of excellent quality for interpretation with the exception that overlying gas shadows obscure the lower pole Routine *preparation includes cleansing enemas, if necessary, one or two days prior to the* procedure The patient is given one or two ounces of castor oil in the late afternoon preceding the day of examination Fluids and food are withheld after midnight The patient is encouraged to be up and about as much as possible before the procedure which aids in the expelling of flatus Prostigmine is also

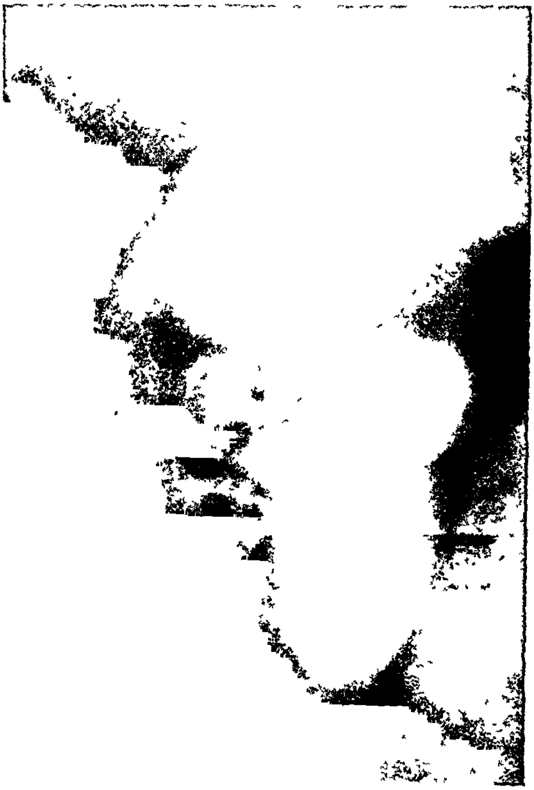

FIG. 2. Overlying gas shadows obscure lower pole distorting otherwise perfect nephrogram.

given at one-half hour intervals for three or four doses in some cases. A preliminary film is always taken and the procedure postponed if the patient is not adequately prepared. A mild sedative is administered and supplemented with demerol 50–100 mg. intramuscularly in some cases.

Technique. We use a technique similar for the most part to that reported by Florence and Weens and also Leighton. After routine cystoscopic inspection of the bladder, one or both ureters are catheterized with bag ureteral catheters. The catheters are inserted well into the abdominal portion of the ureter (approximately 15–20 cm.) so as to preclude their slipping out. The cystoscope is then removed, leaving the catheters in situ. Inflation of the bag is carried out by slowly injecting 0.5 cc of skiodan through the catheter lumen using a Luer-Lok syringe and 20 gauge needle. A definite resistance can usually be felt while inflating the bag. If some resistance is not encountered, one should be suspicious of a puncture in the bag. Except in dilated ureters, it is important not to inflate the bag with more than 0.5 cc of dye in most cases. Overdistention of the bag will cause definite discomfort to the patient and even severe colic in some cases. We have had no trouble when keeping the amount to approximately 0.5 cc in ureters of normal caliber, and this amount has not allowed leakage around the point of obstruction. A hemostat is placed on the end of the catheter to maintain inflation of the bag and taped to the thigh. We have found it necessary to use one or more hemostats directly on the end of the catheter to prevent leakage

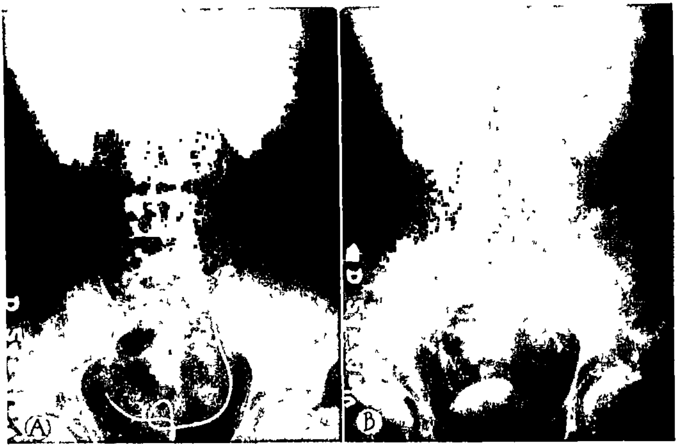

FIG. 3

back through the lumen. Plugging the catheter lumen with rubber tips, tooth picks, etc. was not effective in preventing leakage. There should be no trouble with leakage from the bag itself as long as it is checked by inflation just prior to insertion and caution is exercised against over-inflation. A film is taken to note proper bag inflation and catheter position. A period of 15 minutes is then allowed to elapse prior to the intravenous injection of dye. This will allow a column of urine to collect above the point of obstruction and to fill the upper collecting system. This results in a more rapid concentration of contrast medium in the parenchyma. Figure 3, A illustrates this. Although dye is present in the calyces, there is absence of contrast medium in the pelvis and ureter above the obstructing bags, even though they are located low in the pelvic portions of the ureters. Following the period of waiting mentioned above, 25 cc of 70 per cent urokon is given intravenously. Fifteen minutes following dye injection, a series of films are taken at periodic intervals. The number of films and time intervals will vary with each individual case, depending on when a diagnostic nephrogram appears and what information is desired. In most cases, nephrograms of excellent quality have appeared in 45 to 60 minutes. We usually make exposures at 15 or 30-minute intervals until the desired nephrogram is obtained. When using this procedure for differentiation of an extrarenal mass, the first 15-minute film will often give the desired information. A longer period of obstruction with additional intensification of the renal parenchyma is required when looking for an early or obscure renal lesion. The patient may be moved from the x-ray or cystoscopic table in between films if so desired. After satisfactory nephrograms are obtained, the bag is deflated, the catheter removed and the patient placed in the upright position. Another film is then taken. Release of the contrast medium will often allow excellent filling of the upper collecting system and urinary bladder in addition to the nephrogram. Figure 3, *B* shows the same case as in *A* after removal of the bag catheters, and the patient placed in the upright position. Note the good filling of the upper collecting system and urinary bladder in addition to the nephrograms giving rather striking visualization of all those portions of the urinary tract on one film. The calyces and pelves, which were slightly dilated with obstruction, have immediately come back to a normal contour.

We have obtained the sharpest nephrograms in most cases when using bilateral ureteral obstruction, as would be expected. However, unilateral obstruction on the side in which parenchymal visualization is desired will also give good results although obstruction usually must be maintained for a longer period of time. If, for any reason, a catheter cannot be inserted up the side in which visualization is desired, catheterization and obstruction of the other side should be carried out anyway. Obstruction of the contralateral kidney will often increase the excretion of dye through the unobstructed kidney and give a good nephrogram.

RESULTS

The aforementioned procedure has been performed on 14 patients to date. Nephrograms of good quality for interpretation were obtained in 10 cases. Inadequate preparation of the patient and difficulty maintaining inflation of the obstructing bags were the chief sources of trouble in the four unsuccessful cases. This chiefly occurred early in the series before the technique was properly worked out.

In no instance was it necessary to discontinue the procedure because of discomfort to the patient. Nine of the patients admitted to some sensation of mild pressure in the back or loin. One patient complained of severe colic after inflation of the bag. It was discovered that over 1 cc of dye had been injected into the bag which had markedly overdistended the ureter. This patient tolerated the procedure well after the bag was re-inflated to a lesser amount (0.5 cc). Some of the patients were examined up to 2 hours without onset of pain or distress.

Possible damage to the kidneys must be considered when using a procedure which calls for complete obstruction of the ureter. There has been no evidence of this to date, as judged from followup examination of the urine, blood chemistry, urinary output and excretory urograms in some cases. We have observed transient microscopic hematuria up to five days following this procedure. Evaluation of this is difficult because of the instrumentation involved. Weens and Florence carried out selective phenosulfonphthalein tests in addition to urine examination and excretory urograms on the 8 cases reported by them. They were unable to detect any permanent structural or functional changes in any of their cases. It is well known that ureteral calculi may produce obstruction for a limited period without causing permanent pathologic changes in the kidneys or ureters.

We are unable to report to date any cases in which an obscure lesion was discovered by this procedure in the face of normal pyelograms. We intend to continue to use this procedure in an effort to pick up such a lesion. The nephrograms shown in figure 3 are from a patient in whom a biopsy from a rib showed metastatic carcinoma with strong suspicion that it came from a kidney tumor. Pyelograms were done and appeared normal. Bilateral nephrography was then carried out in an attempt to find an obscure renal tumor giving origin to a rib metastasis. These nephrograms were interpreted as normal. In view of these negative findings, we feel that the metastatic lesion is not originating from a primary tumor in the urinary tract. The patient will continue to be followed closely to see if these conclusions are substantiated. A case of "essential hematuria" showed normal nephrograms by the obstructive technique and is being followed closely for development of a demonstrable lesion. Obstructive nephrography has been of value in several cases where differentiation of an extrarenal mass was required. In the past, we have relied on retroperitoneal air insufflation by the Rivas technique for these problems. Recently we have made use of the obstructive nephrogram and have found it to be most satisfactory, particularly in extrarenal masses that are immediately adjacent to the kidney where air insufflation would still not show a good demarcation between the kidney and the mass. We have been misled on one occasion, however, even when using obstructive nephrography in this type of case. This patient had a palpable mass in the left upper quadrant. Pyelograms showed downward displacement of the left kidney with distortion of the upper calyces. Figure 4 shows an obstructive nephrogram of the left kidney in this patient after one hour. It can be noted that there is an irregular line of demarcation between normally functioning kidney and apparently nonfunctioning tissue at the superior pole represented by a radiolucent mass. On the basis of this interpretation, the left kidney was ex-

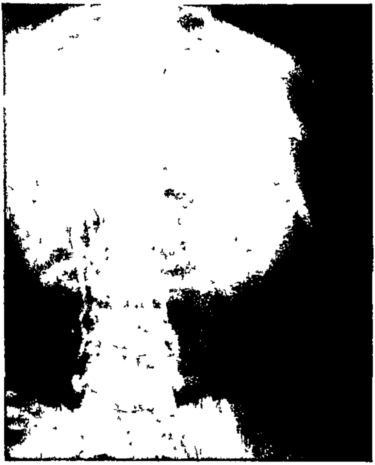

FIG 4

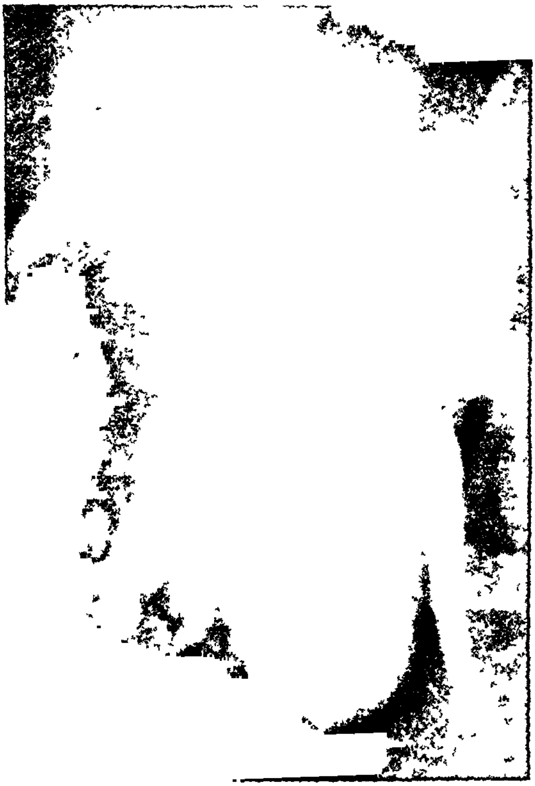

FIG. 5

plored with a preoperative diagnosis of renal tumor. At surgery, a large pancreatic cyst was encountered which was impinging directly on the superior pole of the left kidney and had caused definite indentation and atrophy through pressure. The upper pole of the kidney, seen at surgery, was dark indicating vascular and parenchymal compression.

Figure 5 shows a 45-minute obstructive nephrogram in a patient with calcification in the right kidney. The pyelograms in this patient were within normal limits as were urine culture studies, including those for tuberculosis. The nephrogram shows the calcification to be in the cortex of the kidney and surrounded by a radiolucent zone. There is a strong suspicion of a calcified renal tumor in this case, although calcified cyst or tuberculoma cannot be ruled out. This patient was reluctant to submit to surgery and has since moved to another city. The nephrograms in this patient also illustrate another interesting phenomenon. As can be seen, there is definite demarcation between the cortex and medulla of the kidney with heavier dye concentration in the medullary zone where the tubules of the kidney are situated. In some nephrograms we have obtained, the renal pyramids have also been demonstrated in addition to demarcation of the cortex and medulla. This is at variance with the statement of Weens et al. who found the "cortex attained greater density than the medulla." The intensification of the medulla would be anticipated with the use of this technique and the present concepts of secretion of contrast media and renal function.

Homer Smith states that diodrast, iopax and hippuran (all iodine compounds) are excreted by tubules and have a renal extraction ratio close to 1 0 This would mean that that portion of the kidney which is mostly tubular, namely, the medulla, would have the greatest concentration of the iodine This also explains why the nephrogram is able to be demonstrated by this method in the face of an obstruction which probably produces a back pressure sufficient to stop filtration pressure—the tubules are doing the work

DISCUSSION

Although this procedure has been previously described, it apparently has not gained in popularity as a method for nephrography The limited number of cases reported in which it has been performed is insufficient for any conclusions as to its possible value in the early diagnosis of renal parenchymal lesions It would appear, however, that it has several distinct advantages over other techniques of nephrography It eliminates the necessity for rapid dye injection and immediate x ray exposures for only a limited period, as is the case in aortography and rapid intravenous injection techniques Thus, it will allow careful comparative study of nephrograms for the purpose of picking up small, persistent radiolucent areas which may represent pathological changes not demonstrated on the pyelograms The patient's position may be changed for oblique and other views without the limitation of the time factor The technique is simple and requires no special equipment or training for the urologist The quality of the nephrograms obtained appears to be as good or superior to those obtained by other methods Better delineation between the kidney and an extrarenal mass can be expected when using nephrography The procedure may be of more value than other techniques when information is needed as to the amount of functional renal tissue present, such as in a borderline case being considered for pyeloplasty versus nephrectomy The patients on whom the procedure has been done to date have tolerated it well with no evidence of ill effect or renal damage

There has not been a sufficient number of cases reported to allow complete evaluation or recommendation of nephrography by the obstructive technique Interpretation of these nephrograms with respect to early lesions may prove to be difficult or impractical As in any other method of nephrography or pyelography, the history and clinical findings must be correlated with the other diagnostic data in order to reach the diagnosis The safety of the procedure must be better substantiated We have applied the contraindications to retrograde pyelography to this procedure to date, with an even more conservative attitude with regard to cases where infection or diminished renal function is present Although the technique takes more time than other methods, it is believed that this is offset by the other advantages obtained It is not intended to minimize the value of the other methods of nephrography mentioned Each has its definite value in a particular case

SUMMARY

Experience and results with the technique of obstructive nephrography using bag ureteral catheters done on a limited number of cases have been reported

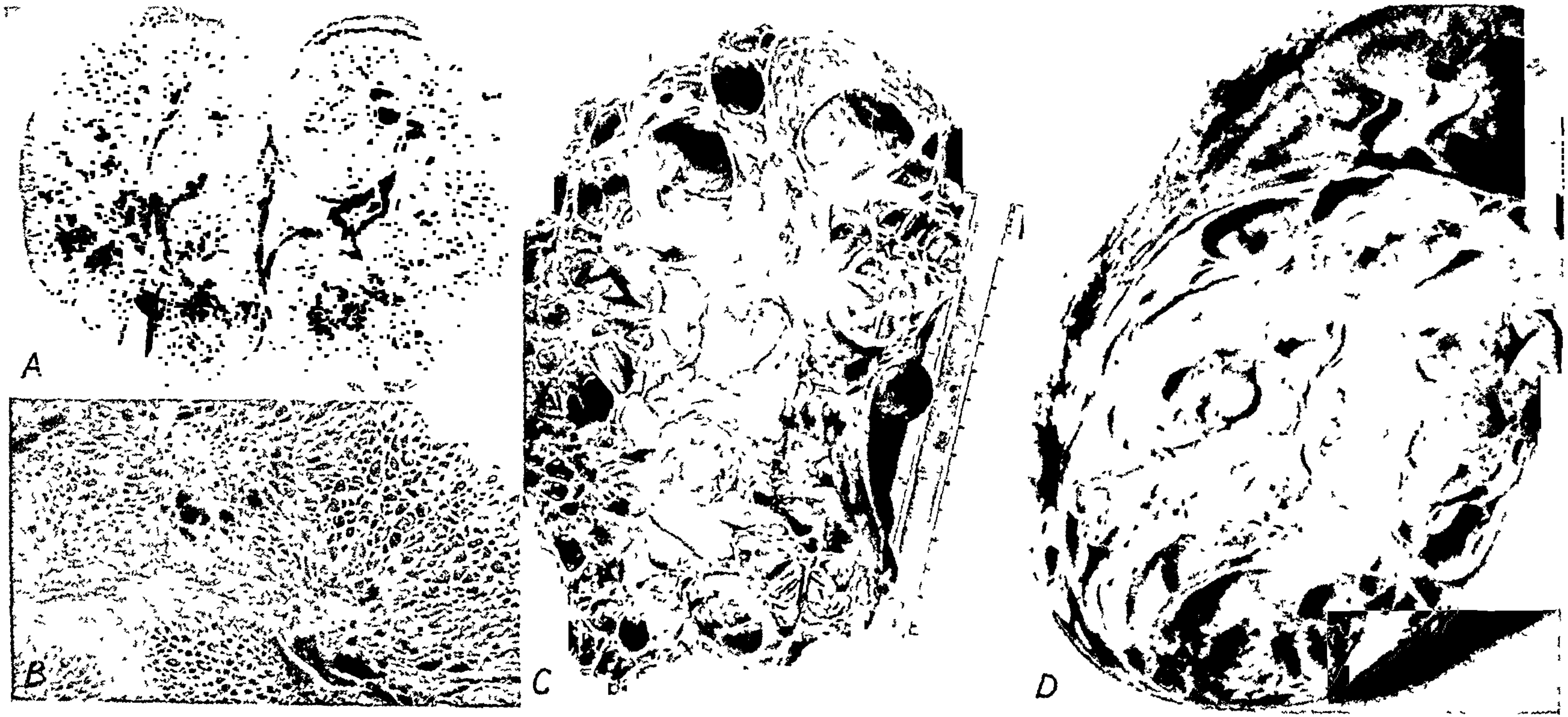

Fig. 1. Types of cystic disease from which "multicystic kidney" should be differentiated. *A*, infantile polycystic kidneys. *B*, closeup view of same. (*A* and *B* from Anderson's *Pathology*, 2nd ed., St. Louis, C. V. Mosby Co., 1953, courtesy of Dr. Anderson and the publishers.) *C*, adult form of polycystic kidney. *D*, multilocular cyst. Upper third of kidney appears normal. (Courtesy of Dr. T. H. Frazier.)

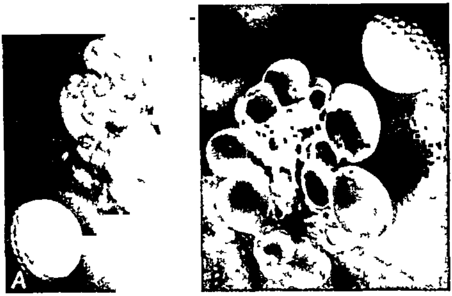

FIG 2 Case of Bunge and Harness reported as "unilateral polycystic kidney in an infant" (J Urol, 65 973, 1951) Appearance and description resemble multicystic entity

From the above description it is apparent that the condition we are discussing has many unique characteristics in addition to its unilateral occurrence which justify setting it apart from the commonly recognized polycystic kidneys (fig 1, *A*,*B*,*C*) In both the infantile and adult forms of the latter, the reniform contour of the organ and the calyceal pattern (although distorted) are retained and on microscopic section varying amounts of relatively normal appearing nephrons capable of function are interspersed amongst the innumerable cysts The infantile polycystic kidney is sponge like in appearance due to myriads of small cysts of uniform size whereas the multicystic kidney resembles a cluster of grapes with great variation in the size of the cysts which number only a dozen or so at most and the entire mass contains no parenchyma worthy of the name

Multilocular cystic kidney may be distinguished by the fact that 1) the disease process is limited to a portion of the kidney only, so that an obviously normal segment remains uninvolved, and 2) the large cysts are subdivided and partitioned so that we find cysts within cysts with consequent lobule formation (fig 1, *D*) Similarly an otherwise normal kidney containing multiple simple cysts may be recognized easily

Considerable confusion exists in the literature regarding the interrelationships and differences of the renal lesions in which cyst formation is a predominant feature in the clinical and pathologic picture Part of this confusion arises from loose use of the word "polycystic" to include any of the abovementioned types where more than one cyst is present Since in clinical practice the concept of heredity, bilaterality, progression and death is so closely associated with the term polycystic kidney, it is suggested that this designation had best be restricted to what all recognize as true polycystic disease Similarly more discriminating use of the descriptive terms multilocular," 'multiple simple" and "multicystic" as applied in any given case will help unravel the problem of the cystic kidney (fig 2)

ETIOLOGY OF MULTICYSTIC KIDNEY

The urologist is hardly competent to pass upon the validity of the different theories advanced as to the etiology of renal cyst formation In the current literature the original "failure of union" theory of Hilderbrant, the "persistence of vestigal structures" thesis of Kampmeier and the "localized urinary obstruction plus vascular impairment" mechanism postulated by Hepler, all have their adherents and critics. None seems universally satisfactory or acceptable in all cases. If one may be permitted oversimplification for the purpose of correlating these three theories with the clinical behavior of the different types of cystic disorders, it is suggested that Hepler's theory explains multilocular cystic kidney, the theory of Kampmeier best fits in with true polycystic disease, while the "failure of union" between the ureteral bud and the metanephric blastema appears tenable in explaining multicystic kidney.

Actually all that can be stated definitely in this regard is that multicystic kidney is a congenital defect resulting from fetal maldevelopment, *not* on an hereditary basis. Again this is in contradistinction to true polycystic disease in which the etiologic process is not only congenital, but also represents an inherent genetic fault. As a corollary, the finding at operation of an unsuspected true polycystic kidney implies that its mate sooner or later will be similarly involved while the finding of a multicystic or multilocular lesion does not carry the same grave connotation.

CLINICAL PICTURE OF MULTICYSTIC KIDNEY

Most of the reported cases of multicystic kidney are strikingly similar and lead to the following composite picture. On routine abdominal palpation in an otherwise healthy infant, a large unilateral, lobulated, nontender, movable mass is found in the flank. In a few cases vomiting, distention and other gastrointestinal symptoms due to displacement of the bowel by the mass have been present and in a still fewer number, pain in the renal area has led to urologic investigation. Urinalysis and other laboratory studies are normal.

On urography a sizable mass will be revealed as a soft tissue shadow on the plain roentgenogram. Most important is complete absence of excretion of the excretory urographic dye on the involved side associated with a normal appearing kidney on the opposite side. Cystoscopy and attempted retrograde study, when performed in the reported cases, have shown either an absence of the ureteral orifice on the side corresponding to the lesion or a blind termination of a small ureter below the ureteropelvic junction.

There is no predilection for side or sex. While the majority of patients with multicystic kidney have been infants, it is probable that a similar process occurs in adults.

The differential diagnosis includes Wilms' tumor, closed hydronephrosis secondary to ureteropelvic obstruction, true polycystic and multilocular cystic kidney, mesenteric cyst, neuroblastoma, and other nonrenal retroperitoneal masses. Except for Wilms' tumor and hydronephrosis these conditions may be differentiated by complete urologic study. Even if a definite preoperative diagnosis cannot be made, since the treatment of multicystic kidney itself as well as these conditions with which it may be confused is primarily surgical, one need not delay operation in the presence of a normal kidney on the opposite side.

As stated, the treatment of multicystic kidney is nephrectomy after demonstration of a life supporting contralateral kidney. The transperitoneal approach has certain advantages in that early control of blood supply, avoidance of injury to adjacent viscera and abdominal exploration particularly of the opposite kidney is possible. Since multicystic kidney is unilateral, the prognosis is good.

Four case reports of patients emphasizing the above features will be presented followed by a review of the literature and abstracts of the previously reported cases of multicystic kidney.

CASE REPORTS

Case 1. F. M. E., Dallas Medical & Surgical Clinic No. C-9858, a 3-month-old female infant, was referred for urological examination after a left sided abdominal mass had been detected one week previously on routine "well baby examination." The referring physician originally felt that the mass might represent a megacolon but a barium enema showed the colon to be normal except for displacement by a retroperitoneal mass. Palpation revealed a movable, nontender, lobulated mass arising in the left flank and extending across the midline of the abdomen and from the costal margin above to the pelvic brim below. Urinalysis and blood counts were normal. A plain film of the abdomen showed a lobulated soft tissue shadow corresponding to the mass felt on physical examination. Excretory urography showed the right kidney to be normal but no dye excreted on the left through a 30-minute exposure. At cystoscopy the left ureteral orifice could not be found after prolonged search. A roentgenogram of the chest was interpreted as normal.

At this point, although the exact diagnosis was in doubt, it was felt that further investigation would not be fruitful, so surgical exploration was decided

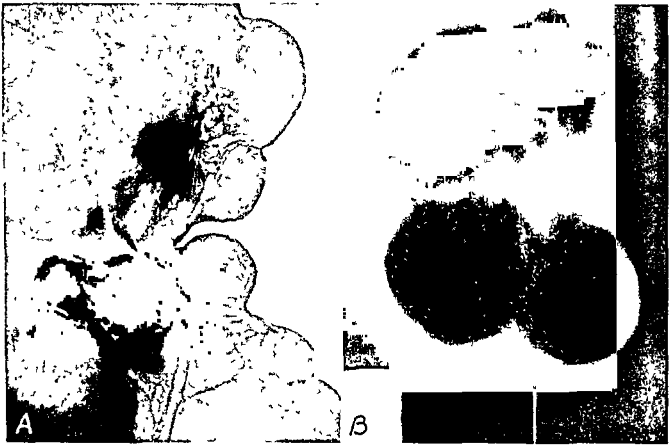

FIG. 3. Case 1. *A*, surgical specimen. *B*, attempted injection showing stenotic ureter with little or no dye entering cysts.

upon with a preoperative diagnosis of cystic disease of the kidney, Wilms' tumor, or hydronephrosis as the most likely possibilities.

Under general anesthesia the peritoneum was opened through a left transverse incision at the level of the umbilicus. As anticipated, the mass was found to be retroperitoneal in position with the left colon displaced medially. By blunt and sharp dissection, a lobulated cystic structure consisting of about 6 or 8 massive cysts was freed up and removed intact after severing a definite pedicle. The ureter entered the midportion of the mass. The colon was returned to its normal bed and the wound closed with a small drain to the retroperitoneal area. Convalescence was uneventful and followup examination 2 years later showed the child in excellent health.

Gross examination of the specimen revealed a multicystic structure weighing 465 gm. (fig. 3). It bore no relation to a normal kidney and in only one small focus was any tissue grossly identifiable as renal tissue found. On section, multiple thin-walled cysts ranging in size from 1 cm. to 5 cm. were found. The lining of the cystic structures was smooth and grayish white in color. A short length of ureter emerged over the cystic lower pole and was marked by a point of constriction at the ureteropelvic junction region. On microscopic examination

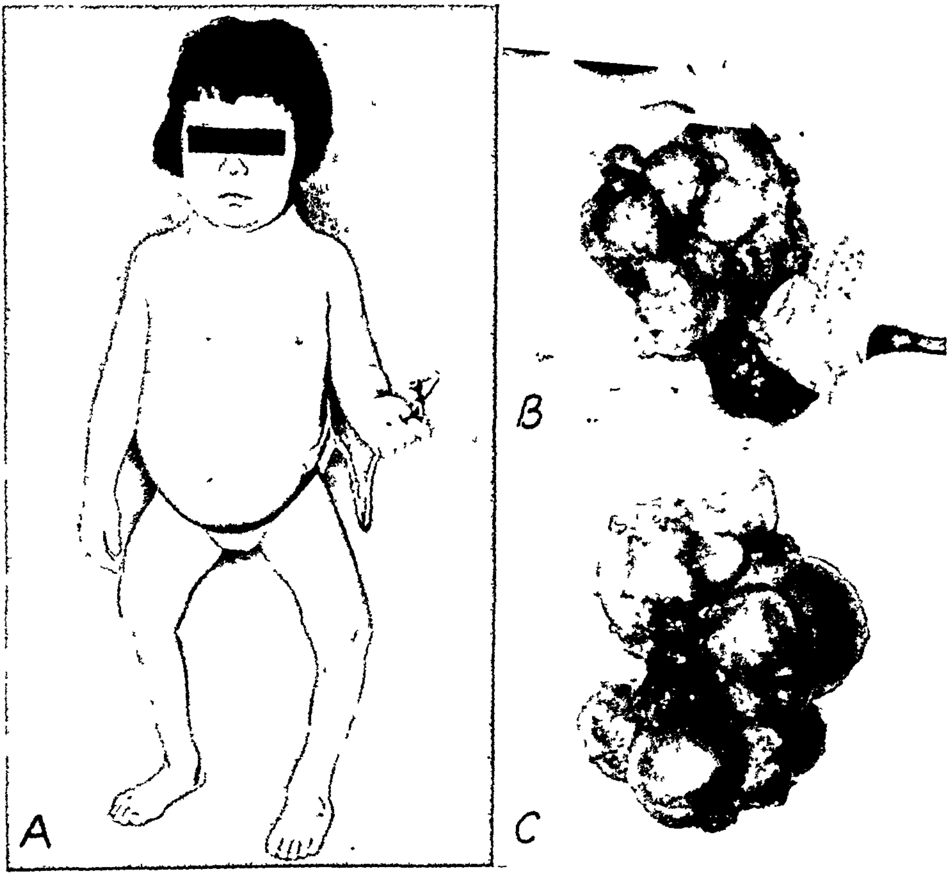

FIG. 4. Case 2. *A*, appearance of 4-year-old girl with renal rickets after left nephrostomy for hydronephrosis. *B*, exploration on *right* revealed multicystic kidney. *C*, surgical specimen.

a few remnants of renal parenchyma were found which were interpreted as showing fibrotic atrophy and dilation of the tubular structures Abundant collagenous tissue formed the walls separating the cystic spaces which were lined by a single layer of flattened cells The ureter possessed a lumen with the diameter markedly narrowed The pathologist returned a diagnosis of "polycystic disease of left kidney with fibrotic atrophy of small portions of persisting parenchyma" but agreed that the structure differed fundamentally from the usual form of polycystic kidney and stated that the term was used in a descriptive sense only.

Case 2 J L V, Texas Children's Hospital No 15999, was a 4-year-old girl who was admitted to the hospital with a probable diagnosis of renal rickets General appearance of the child is shown in figure 4, *A* The abdomen was enlarged but no masses were palpable Laboratory investigation revealed blood urea nitrogen of 132 mg per cent, serum chloride 91 mEq, serum phosphorus 6 5 mg per cent, serum calcium 9 0 mg per cent, serum phosphatase 9 7 K-A units, creatinine 3 54 mg per cent The urinalysis was negative except for a trace of albumin Cystoscopic examination revealed a normal bladder with normal appearing ureteral orifices The ureteral catheter was passed to the left renal pelvis and a retrograde pyelogram showed marked hydronephrosis secondary to ureteropelvic obstruction On the right the ureteral catheter passed for 10 cm but no dye could be injected beyond the tip of the catheter A pyeloplasty with nephrostomy was carried out on the left side and the child did reasonably well

It was felt that in all probability the right kidney was hydronephrotic also and since preservation of all possible parenchyma was imperative in this child, the right kidney was explored surgically 2 weeks after the pyeloplasty To my surprise, no hydronephrosis was found but the right kidney was replaced by a multicystic mass with no recognizable renal parenchyma (fig 4, *B*) The ureter was represented by a fibrous cord in its upper portion but acquired a small lumen in its lower two thirds Only a few attenuated blood vessels supplied the mass, which was easily removed and the wound closed in routine fashion

Examination by the pathologist showed the right kidney measuring 5½ by 3½ by 2 cm (fig 4, *C*) It was composed of varying sized thin-walled cystic spaces 1 to 2 cm in diameter Each cystic space had a smooth inner lining and a wall about 1 mm in thickness The pelvis was not identifiable The cysts were closely packed and separated by small amounts of fibrofatty tissue On microscopic section the cysts were seen to be lined by a flattened layer of cells No glomeruli were noted, but small, slightly dilated tubules, embryonic in type, were found The upper ureter was nonpatent Inflammatory changes were conspicuous by their absence As a matter of interest, this child has been re examined 3 years later and is in reasonably good health, although the bone changes and blood chemistry findings characteristic of renal rickets are still present It is felt that this case represents a rare combination of obstructive hydronephrosis on one side with a multicystic kidney on the other The diagnosis of the pathologist was "polycystic disease of right kidney" although it is apparent from the description that this is in no sense the typical form of polycystic kidney disease

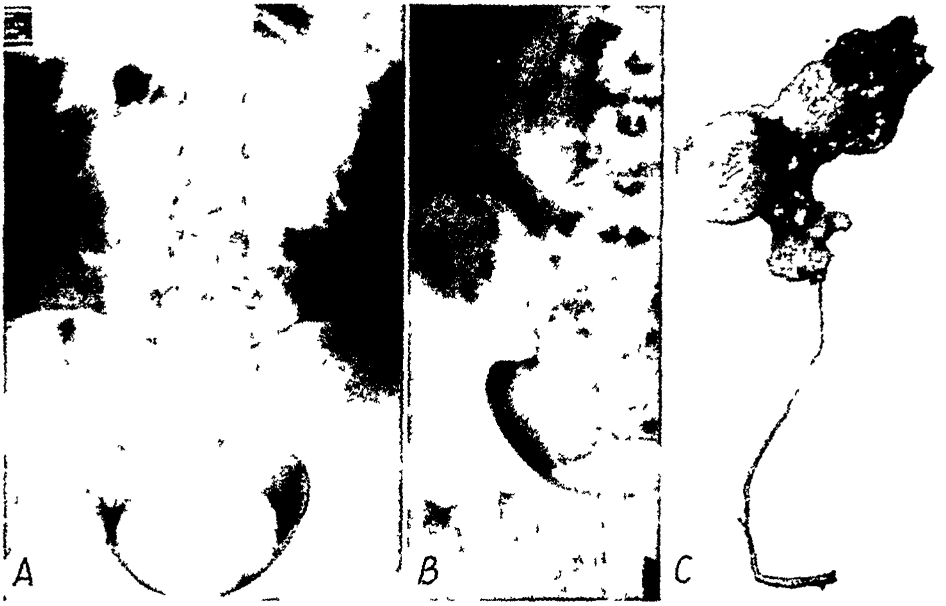

FIG. 5. Case 3. A, excretory urogram showing hypertrophied left kidney and nonfunction on right. B, small, short, blind ending right ureter. Note calcific ring shadow in renal area. C, operative specimen; upper two-thirds of ureter was nonpatent cord.

At the pyeloplasty on the left the kidney showed typical hydronephrosis with no evidence of polycystic disease.

Case 3. Miss M. M., Parkland Hospital No. 114709, a 21-year-old Latin American girl, complained of pain in the right flank of 2 weeks' duration. There was slight tenderness to palpation in the right renal area and the right lower quadrant, but no mass could be felt. Routine laboratory studies were normal. After excluding appendicitis, cholecystitis, and pathological process of the pelvic organs by appropriate studies, urologic examination was carried out. On a plain film of the abdomen the right renal outline could not be visualized. On excretory urography there was prompt excretion of the contrast material on the left revealing a somewhat hypertrophied but otherwise normal left kidney (fig. 5, *A*). At no time during the examination, including delayed exposures, was there any contrast material seen on the right side. The most striking finding on the right was the presence of an ovoid density having a thin peripheral shell of calcium lying just to the right of the filar shadow beneath the twelfth rib and measuring 3 by 4 cm. in diameter. On cystoscopic examination the bladder appeared normal with two normal appearing ureteral orifices. On the right side all catheters met an impassable obstruction 10 cm. above the ureteral orifice. Repeated attempts to inject skiodan through the right ureteral catheter resulted in visualization of only the lower 10 cm. and the caliber of this segment appeared smaller than normal (fig. 5, *B*).

In view of these findings, a diagnosis of probable multicystic kidney was made and the right renal area was exposed through a lumbar incision. Lying within Gerota's fascia, imbedded in perirenal fat, a fibrocystic structure measuring 3 cm. in diameter was found which apparently represented the right kidney. The vessels composing its vascular supply were of very small caliber. A thread-like structure representing the ureter was traced downward over the brim of the pelvis where it became tubular and contained a lumen (fig. 5, *C*). Convalescence was satisfactory and the patient has been free of pain for the ensuing one year.

Pathologic examination: On section the cyst walls were composed of hyalinized collagenous tissue with duct structures lined by epithelium resembling the transitional type found in the urinary tract. Surrounding some of the larger ducts, small tubules identical with the connecting tubules of the adult kidney were found, many of which contained colloid eosinophilic material. The pathologic diagnosis was "hypoplastic kidney." The proximal end of the ureter was simply a fibrous string while distally it contained a small lumen. This specimen does not represent the usual form of multicystic kidney, neither does it correspond to the typical hypoplastic kidney. The presence of cysts, the absence of normal kidney parenchyma, and the atresia of the upper ureter lead me to feel that it probably represents a variation of multicystic kidney and it is for these reasons that it is included in this paper.

Case 4. Mrs. I. F., Northwest Texas Hospital No. 148072. I am privileged to report this case through the courtesy of Dr. Jan R. Werner, who has kindly made available to me his urograms, operative note and pathological report. The patient was aged 70, the mother of 10 children, who underwent urologic investigation because of recurring bouts of pyuria. She had undergone hysterectomy at the age of 40 and cholecystectomy at the age of 60 for acute cholecystitis, at which time a gallbladder containing 110 stones was removed. Physical examina-

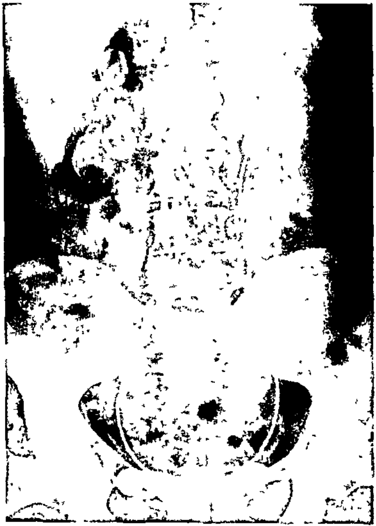

FIG. 6. Case 4. Retrograde urogram showing termination of right ureter at 10 cm. level and calcific ring shadows in corresponding renal area. Normal left pyelogram.

tion was irrelevant except for the surgical scars and a large cystocele and rectocele. A catheterized urine specimen showed 15 to 20 pus cells and red blood cells. A culture showed E. coli and an acid-fast stain and culture were negative. A plain film of the kidneys, ureters, and bladder showed multiple large, round, ringlike, calcific lesions located in the region of the right kidney. Their retroperitoneal location was confirmed by a lateral film. An excretory urogram showed the left kidney to be normal in structure and function, but no excretion of dye was demonstrable on the right. Cystoscopy showed diffuse chronic cystitis and urethritis. Both ureteral orifices were visualized and catheterized. The ureteral catheter was passed to the left renal pelvis without obstruction and the specimen of urine from this side was negative on microscopic examination and sterile on culture. On the right all catheters met a definite obstruction 16 cm. above the bladder. Several attempts to inject dye beyond this point, including the use of a bulb to occlude the ureteral orifice, were unsuccessful (fig. 6).

In view of the history and findings, exploration of the right renal area was felt indicated and was carried out through a right lumbar incision with removal of the twelfth rib. The previously demonstrated conglomeration of calcific shadows was readily identified as being imbedded in the perirenal fat and no kidney as such could be found. The proximal end of the ureter terminated at a point corresponding the level of obstruction met at cystoscopy. Above this point the ureter became obliterated and finally disappeared into the surrounding fibrous tissue. The entire mass was dissected free and removed and the wound closed in routine fashion. The patient made a satisfactory convalescence.

On pathologic examination of the specimen by Dr. J. V. Denko the specimen measured 8.5 by 5.5 by 2 cm. and consisted of a stony hard, lobulated mass of fat, connective tissue and cystic structures with calcific outer rims. On microscopic examination tubular structures compatible with embryonic renal tissue were found. The cyst walls consisted of collagenous tissue in which there were calcific deposits. The diagnosis of the pathologist was "embryonic mesonephric renal tissue with regional fibrocalcific nodules." From the appearance of the urograms, the atresia of the ureter and the gross appearance found at operation by Dr. Werner, I am inclined to believe that this represents a multicystic kidney in an adult.

REVIEW OF LITERATURE

A review of the literature reveals 15 cases which I believe can be classified acceptably as examples of congenital unilateral multicystic kidney (table 1). Some of these have been considered by their authors as instances of unilateral polycystic disease, but their descriptions and illustrations appear more characteristic of the multicystic variety (fig. 2). The same may be said of some cases considered by the reporting urologist to be examples of multilocular cystic kidney and one recent case described as multiple simple cysts. I have excluded from the list several case reports of obviously multilocular cysts which previous writers on the subject of multicystic kidney have included in their surveys as identical with the multicystic entity.

For practical purposes the distinction between multicystic kidney and multilocular cyst is not too important inasmuch as the clinical picture is essentially the same in both Since the pathological features and the etiology are different, however, it is suggested that the separation be maintained in subsequent reviews in the interest of unraveling the still confused problem of the kidney in which cyst formation is a predominant feature Certainly both multicystic and multilocular cysts should be classified separately from polycystic disease Not only the gross appearance but also the histologic pattern seems fundamentally different from that generally recognized as polycystic kidney disease

Little attention is devoted in the standard textbooks to multicystic kidney Allen, in his monograph *The Kidney*, shows photographs from two infants age 6 months and 2 weeks which appear characteristic of the multicystic disorder although the accompanying legend labels them as "congenital polycystic kidney " Allen mentions that the photomicrographs of these two cases are different from that found in the usual form of "diffusely polycystic kidney " In *The Urology of Childhood* by Higgins, et al an operative specimen from a male infant of 5 weeks who presented with a mobile lump in the right iliac fossa is shown The kidney was removed by laparotomy after its mate had been palpated and found normal Higgins states that a unilateral polycystic diseased kidney is occasionally encountered in children but probably has no connection with the bilateral form and is perhaps better known as multicystic disease In Gross' *The Surgery of Infancy and Childhood* are found illustrations of two specimens of "unilateral polycystic kidney, removed from two infants" 19 days old and 9 months old *These appear characteristic of multicystic kidney Campbell, in his Clinical Pediatric Urology,* shows an operative specimen which appears typical of multicystic kidney although the accompanying legend states that it is "congenital multilocular cyst of the right kidney in a boy of 4 years the upper ureter was impervious and there were neither pelvis nor calyces " Campbell refers to this and to the cases of Lynch and Thompson, Schwartz, and Ravitch and Sanford as "congenital multilocular cysts," and considers them to be a collection of solitary cysts Campbell emphasizes, however, that the condition is to be differentiated from congenital polycystic disease which characteristically involves both kidneys and from cystadenoma of the kidney

SUMMARY

The condition designated by Schwartz in 1936 as "multicystic kidney" which consists of replacement of normal kidney by a conglomeration of varying sized cysts with no discernible renal parenchyma often associated with absence or atresia of the ureter should be regarded as a separate entity to be distinguished from polycystic kidney disease and multilocular cysts of the kidney The typical clinical picture consists of the finding of a mass in the renal area in an otherwise healthy infant with nonfunction on the excretory urogram on the involved side in association with a normal contralateral kidney It is probable that a similar lesion occurs in adults The treatment is nephrectomy and the prognosis is good

The previously reported cases in the literature are abstracted and four personal cases presented

A plea is made for recognition and proper designation of multicystic kidney in future reviews of renal cystic disorders.

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PRIMARY KIDNEY TUMORS OF CHILDHOOD

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The challenging problem of the management of kidney tumors in children led to a review of the patients found to have such tumors in the past 25 years on the urological and surgical services of the Children's and the Western Pennsylvania Hospital in Pittsburgh There were 59 patients with Wilms' tumor, 3 patients with a papillary adenocarcinoma of the kidney and 2 patients with renal cell carcinoma

WILMS' TUMOR

The diagnosis in 49 patients was made from the tissue histology* and in the remaining 10 cases by reasonable clinical evidence In the past 25 years at Children's Hospital there was one Wilms' tumor for every 1787 admissions and, as is the consensus of opinion, it was second in frequency to neuroblastoma among the malignant neoplasms of childhood As is usual in congenital lesions, there was found no predilection for sex or side, but there is apparently for race, although this may be due to the greater number of the white race being admitted to these hospitals (fig 1) Thirty-two of the patients were females and 27 were males There were 54 white children, 4 Negroes and 1 Oriental The left kidney was involved 30 times and the right 25 times Bilateral Wilms' tumor is considered quite unusual, but because of the incidence of 4 cases, or 7 per cent, we believe that it is more common than has been thought previously

The symptoms and signs manifested by the reported Wilms' tumors (table 1) follow the generally accepted trend except in a few instances In this series the incidence of hematuria is lower, occurring in but 7 cases and in 2 of these it was microscopic only Albuminuria occurred in only 15 patients out of fifty-nine Nine patients had pyuria of varying degree Abnormal urinary habits occurred infrequently in this series The statistics of the incidence of hypertension are invalid in this study as the blood pressure was not recorded consistently The duration of symptoms before diagnosis (table 2) in the reported cases varied from less than 1 week to 2½ years

It is our opinion that development of a standardized treatment for Wilms' tumor is necessary so that valid statistical data in larger series may be accumulated toward the goal of lowering the mortality rate However, we are also beholden to attempt an evaluation of any new therapeutic means that presents itself Prompt diagnosis, using all available urological means, with the least possible handling of the tumor, correction of anemia and stabilization of fluid

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Read at annual meeting, American Urological Association, Los Angeles, Calif May 18, 1955

* All pathological diagnoses restudied and confirmed by Dr George H Fetterman, pathologist to Children's Hospital or Dr Allen Graham, pathologist to Western Pennsylvania Hospital

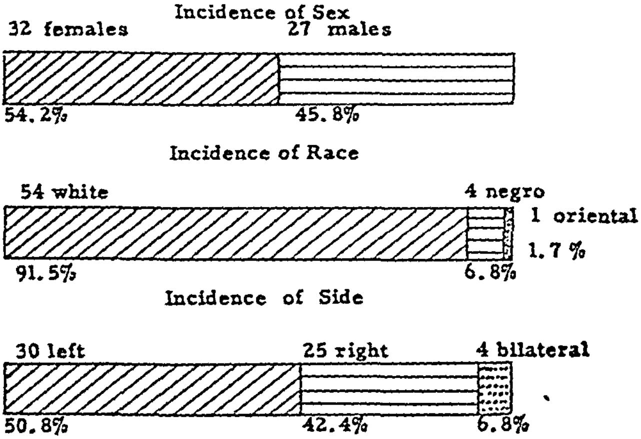

FIG 1

TABLE 1 *Signs and symptoms in 59 patients with Wilms' tumor*

Anemia	59	Pallor	5
Leukocytosis	46	Abdominal varices	5
Mass in abdomen	39	Hypertension	4
Fever	20	Pain in leg	3
Metastasis	18	Diarrhea	3
Pain in abdomen	17	Gaseous distention	2
Albuminuria	15	Night sweats	1
Anorexia	15	Jaundice	1
Enlarged abdomen	14	Edema of genitalia	1
Loss of weight	13	Joint pains	1
Nausea and vomiting	13	Acute urinary retention	1
Pyuria	9	Tenesmus	1
Hematuria	7	Urgency	1
Irritability	6	Ascites	1
Malaise	6	Pain in chest	1
Constipation	6		

TABLE 2. *Duration of symptoms of 59 patients with Wilms' tumor*

Number of months	Less than one week	1/4	1/2	3/4	1	2	3	4	5	6	12 to 30
Number of patients	11	5	7	2	14	7	5	2	1	2	3

balance followed by transperitoneal nephrectomy with prior vascular pedicle and ureteral ligation; block dissection of the tumor, with removal of vena caval tumor thrombi extension if necessary and postoperative radiation therapy are well accepted as the best standardized treatment to date. Radiation of the tumor site, however, leaves much to be desired, as seldom in our experience does Wilms' tumor recur in the renal fossa, but rather appears as a distant metastasis particularly in the lungs. Total radiation therapy, particularly in infants and children, is not feasible because of the marked depression of the bone marrow resulting in aplastic anemia. Therefore, a method must be sought which is lethal to distant small cellular metastases, yet promises a low morbidity.

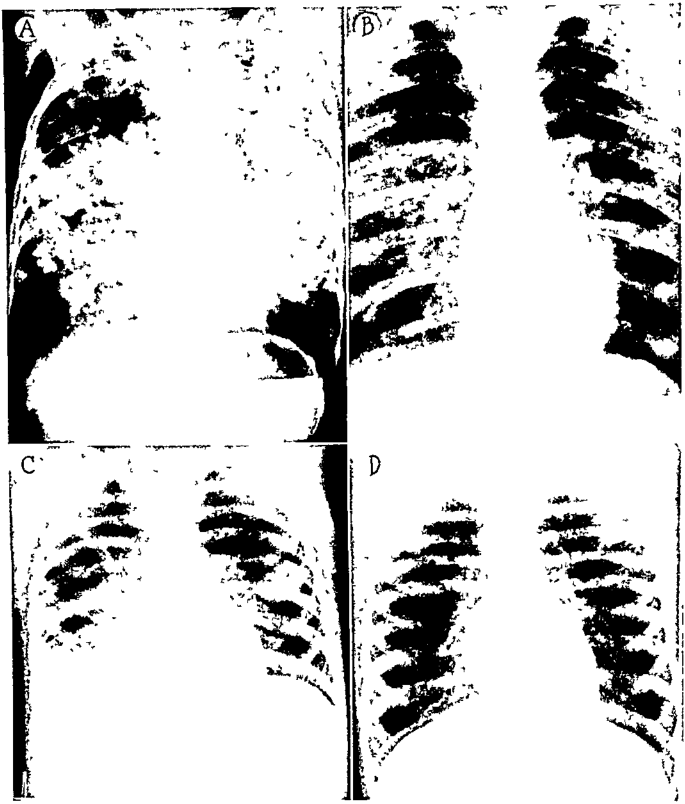

FIG. 2

Following the trial use of intravenous nitrogen mustard in patients with extensive metastasis from Wilms' tumor there was occasionally visible evidence of tumor regression (fig. 2). This work was done by Dr. Paul Gaffney of the Children's Hospital. It was postulated, therefore, that if a large tumor mass could be partially destroyed, smaller, invisible metastatic tumor masses or individual cells that occurred preoperatively or at operation, could possibly be destroyed before growth began. Intravenous nitrogen mustard in a dosage of 0.4 to 0.8 milligram per kilogram of body weight is given, therefore, in the immediate postoperative period and followed in 2 to 3 weeks by radiation therapy to the operative site. The only untoward reaction is a marked rise in the blood uric acid content when there is marked tissue destruction. Removal of the

TABLE 3. *Types of therapy administered to 59 patients with Wilms' tumor*

	Died of Wilms' Tumor	Alive less than		Alive 2 to 5 years	Alive longer than 5 years	Total
		1 yr.	2 yrs.			
Nephrectomy only	1	—	—	—	1	2
Nephrectomy and postoperative radiation .	14	4	4	1	3	26
Preoperative radiation and nephrectomy	2	—	—	—	—	2
Preoperative radiation, nephrectomy and postoperative radiation	1	—	—	—	—	1
Radiation only	17	—	—	—	1	18
Biopsy	6	—	—	—	—	6
None	4	—	—	—	—	4
Nitrogen mustard*	(7)	(3)	(3)	(1)	—	(14)
	45	4	4	1	5	59

* Included in category 2 and 5.

large primary tumor mass obviates this. This is of necessity a clinical study, as *in vitro* trial is not feasible because of the instability of nitrogen mustard in solution. Admittedly the number of patients treated in this manner is small and of too short duration for any conclusions to be drawn, but it appears to us to offer hope for the future and it is anticipated that with accumulation of more data some definite opinion may be expressed.

Treatment of the 59 patients with Wilms' tumor was supervised by a number of physicians and, therefore, differed with each therapeutic school of thought. As can be seen graphically (table 3), the majority of patients received either radiation therapy alone or nephrectomy followed by radiation therapy. The 18 patients who received radiation therapy alone were considered inoperable and/or had extensive metastasis. The dosages varied from 1500 to 7700 air roentgen units. Thirty-one patients underwent nephrectomy; two received no radiation therapy; two, preoperative radiation; 26, postoperative radiation; and one, both types of radiation therapy. A new adjunct to the therapy of Wilms' tumor, intravenous nitrogen mustard, was used in the treatment of 14 patients.

Of the 49 patients treated, 14 are now living (table 4). One patient with proved Wilms' tumor has survived over 8 years following radiation therapy alone. Thirty-one patients had a nephrectomy. One patient who has lived 6 years had a nephrectomy only. The remaining 12 patients who have had a post-treatment life span from 2 months to over 8 years, all underwent nephrectomy plus postoperative radiation therapy. In all but one the surgical approach was transperitoneal. Of the patients treated with intravenous nitrogen mustard 7 are now living. Of the 7 patients who died, 6 had metastatic involvement at the time of nitrogen mustard therapy. In 2 of these it was given as an adjunct to radiation therapy only and in 5 following nephrectomy.

Upon what may we base the prognosis in Wilms' tumor? It is generally agreed

TABLE 4 *Group of 14 living Wilms' tumor patients*

Age at time of Diagnosis	Duration of Symptoms	Type of Operation	Pre operative Radiation (air roentgen units)	Post operative Radiation (air roentgen units)	Time Elapsed since Treatment
		Survival Over 2 years			
1½ mos	2 wks	Transperitoneal nephrectomy	None	1513 r	8 yrs 9 mos
3¾ mos	2 wks	Laparotomy and biopsy	None	2280 r	8 yrs, 7 mos
8 mos	2 wks	Transperitoneal nephrectomy	None	None	6 yrs
3½ mos	1 wk	Transperitoneal nephrectomy	None	3002 r	5 yrs, 3 mos
4½ mos	3 mos	Lumbar nephrectomy	None	5742 r	5 yrs
2 yrs 2 mos *	2 wks	Transperitoneal nephrectomy	None	2078 r	2 yrs, 10 mos
		Survival Under 2 years			
1 yr 5 mos *	2 dys	Transperitoneal nephrectomy	None	6496 r	1 yr, 1 mo
7½ mos	2 wks	Transperitoneal nephrectomy	None	4950 r	1 yr, 1 mo
4 yrs 2 mos *	5 mos	Transperitoneal nephrectomy	None	4900 r	1 yr, 1 mo
2 yrs *	2 dys	Transperitoneal nephrectomy	None	5309 r	1 yr
9 mos	1 day	Transperitoneal nephrectomy	None	585(?) r	10 mos
1 yr 5 mos *	1 day	Transperitoneal nephrectomy	None	5842 r	2 mos
8 yrs 4 mos *	1¾ mos	Transperitoneal nephrectomy	None	6746	2 mos
2 yrs 3 mos *	2 dys	Transperitoneal nephrectomy	None	5020 r	2 mos

* Nitrogen mustard therapy

that size of tumor and histological makeup have no bearing on prognosis Are there other factors that may? The age at the time of diagnosis of Wilms' tumor, in this series, varied from 2 months to 14 years (table 5) averaging 36½ months In contradistinction to this, all patients living more than 1 year averaged 14½ months of age at time of diagnosis and those surviving more than 2 years averaged 8¼ months of age We believe, therefore, that the younger the patient and thus the younger the congenital Wilms' tumor the better the prognosis The duration of symptoms is difficult to evaluate as so much depends upon the acuity and interest of the parents, their economic status, the availability of medical advice and the physicians' awareness of the potentialities of the presenting symptoms The average duration of symptoms in all patients was 10 weeks while in those living more than 1 year it was 4½ weeks and in those living more

TABLE 5. *Age at time of diagnosis of 59 patients with Wilms' tumor*

Number of months...	2	3	4	5	6	7	8	9	11	12 to 16	16 to 20	20 to 24
Number of patients..	1	1	2	1	1	1	4	1	1	6	3	1
Number of months...	24 to 30	30 to 36	36 to 42	42 to 48	48 to 54	54 to 60	72	81	100	115	138	168
Number of patients..	6	7	5	4	2	4	3	1	1	1	1	1

TABLE 6. *Number of months between diagnosis of Wilms' tumor and death in 45 patients*

Number of months	1/4	1/2	3/4	1	2	3	4	5	6	7	8	9	12	13	15	16	33	54
Number of patients........	2	2	1	1	5	6	7	3	5	2	1	2	2	1	2	1	1	1

than 2 years it was 3½ weeks. Thus it is felt that generally the earlier the treatment is instituted following significant symptoms the better the chance of survival. Gross hematuria and abdominal pain are considered of grave import as only 1 patient out of 7 with the former and 1 patient out of 17 with the latter symptom are living. Of the 45 patients who died (table 6), 32 were dead 6 months after the diagnosis was made. After 2 years post-treatment survival a patient is considered a probable cure but this is not an absolute fact as 1 patient in this group died from metastasis 4½ years after the diagnosis was made. The other death after 2 years was due to anesthesia, at which time there was no evidence of metastasis.

The cases of bilateral Wilms' tumor are thought to be of sufficient interest to report individually.

Case 1 (13361 C.H.). A 7-month-old girl had had a gradual increase in the size of her abdomen for 4 months without an increase in weight and with development of pallor. On examination two masses extending from costal margin to crest of ilium were felt in both flanks. Retrograde pyelography visualized anatomical distortion of the renal architecture. There was marked secondary anemia and normal renal function. Radiation therapy was advised but refused. She was readmitted 3½ months later in extremis. The diagnosis was confirmed by autopsy.

Case 2 (E-3233 C.H.). An 11-month-old boy was found to have a movable mass in the right abdomen which extended beyond the midline 2½ weeks before admission. On examination a small, firm, movable mass was found in the left renal area in addition. No urography was done. Right transperitoneal nephrectomy was performed removing a Wilms' tumor. Following a postoperative death, autopsy revealed a left Wilms' tumor, also, and generalized abdominal metastasis.

Case 3 (0-2962 C.H.). A 14-month-old boy had recurrent gross hematuria for 1 month before admission. Examination revealed an enlarged left kidney mass. A slight secondary anemia was present. Retrograde pyelography (fig. 3, *A*) visualized a distortion of the left renal collecting system. Left lumbar nephrec-

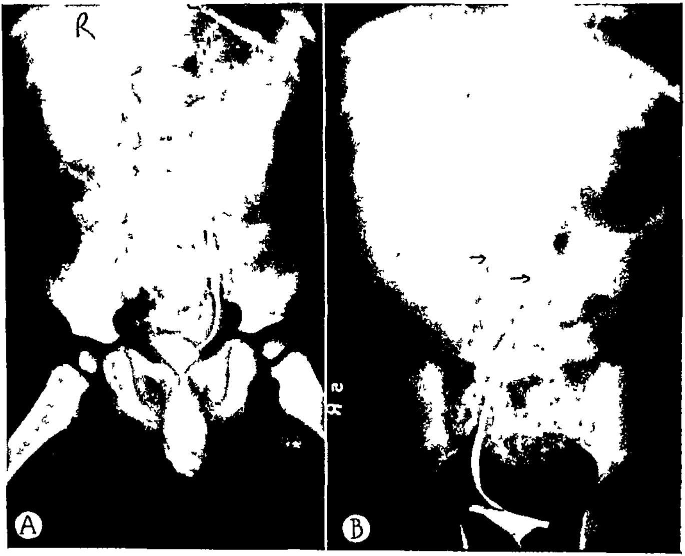

FIG. 3

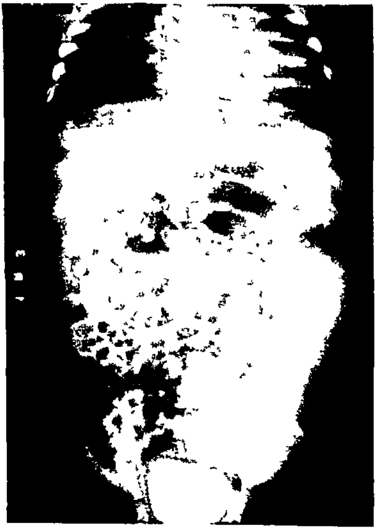

FIG. 4

tomy was followed by radiation therapy. Eight months later a mass was found in the right abdomen. Retrograde pyelography (fig. 3, *B*) showed evidence of a right renal tumor. Two courses of radiation therapy were given with decrease in size of tumor as demonstrated by urography and physical examination. However, pulmonary metastases and irradiation nephritis developed with consequent uremia, oliguria, edema and marked hypertension culminating in death 1¼ years after primary diagnosis. Autopsy was not permitted.

Case 4 (Q 3636 C.H.). A 12½-month-old girl had always had a large abdomen and for 1 month before admission a mass could be felt in each flank. Abdominal examination revealed bilateral masses, the left extending from the flank to the umbilicus, and the right from flank to mid-clavicular line and extending down into pelvis. Excretory urography (fig. 4) visualized bilateral distortion of the renal pelves and calyces. Laparotomy and biopsy established the diagnosis of bilateral Wilms' tumor. Postoperatively, intravenous nitrogen mustard was given, followed by radiation therapy and cortisone. Six months later she died. Autopsy confirmed the diagnosis.

PAPILLARY ADENOCARCINOMA

The diagnosis of papillary adenocarcinoma has been made in 3 patients during the 25 years of this study, and all these within the past 10 years. Adenocarcinoma is quite rare in children, only 10 cases having been reported, and none of these,

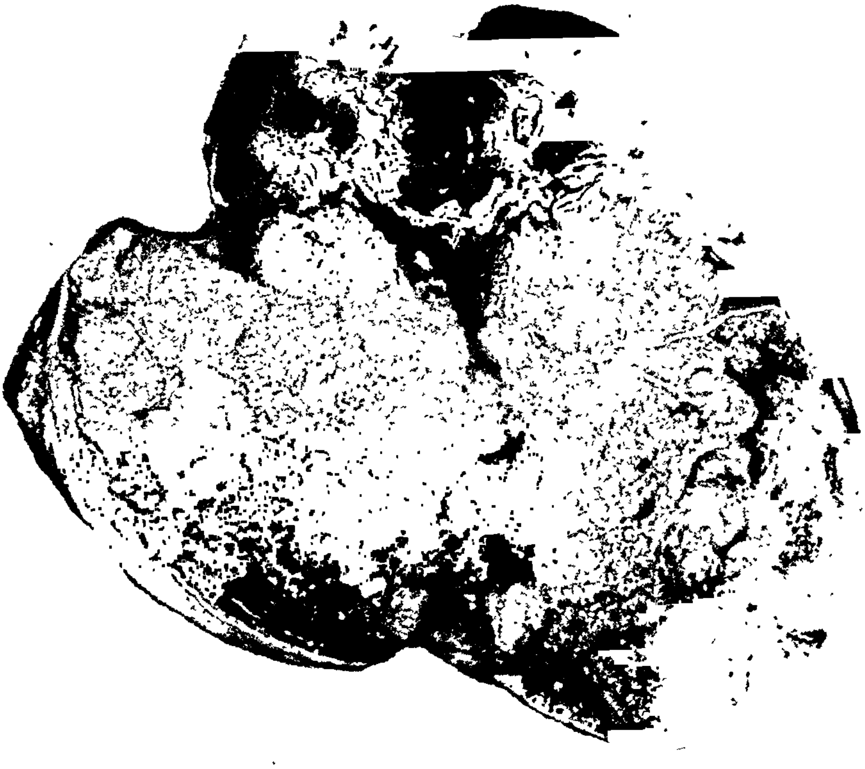

FIG. 5

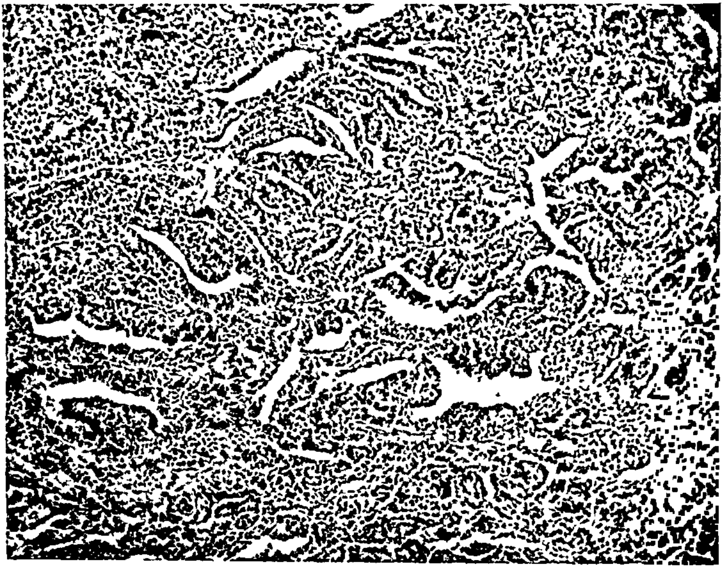

FIG 6

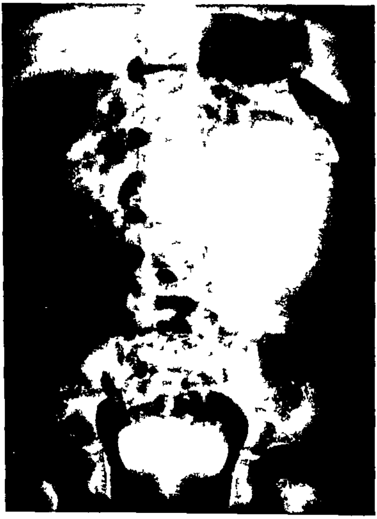

FIG 7

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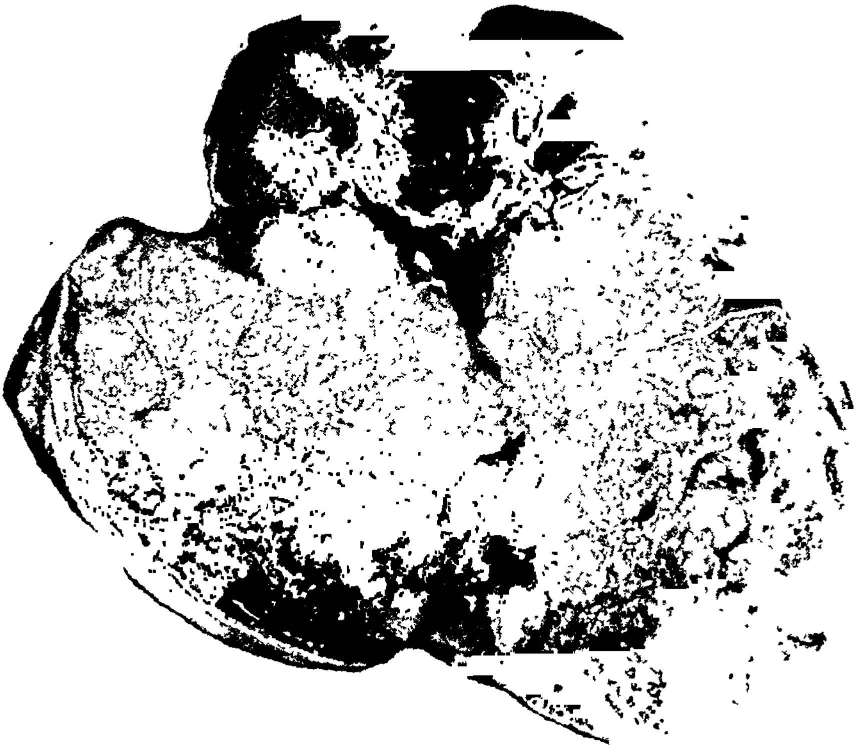

FIG. 5

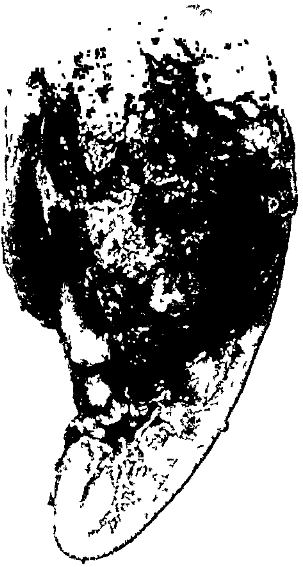

FIG 9

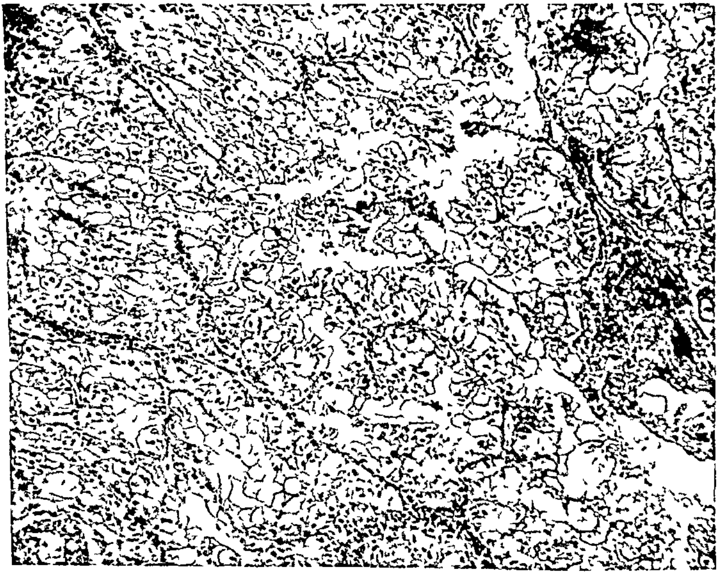

FIG 10

SUMMARY

Data concerning 64 children with primary renal tumors are recorded. These comprise 59 Wilms' tumors, including 4 bilateral tumors; 3 papillary adenocarcinomas and 2 renal cell carcinomas.

Preliminary data on the use of intravenous nitrogen mustard in the immediate postoperative treatment of Wilms' tumor and its rationale are presented.

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SURGICAL MANAGEMENT OF TRANSCAPSULAR RUPTURE OF THE KIDNEY 24 CASES

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Any discussion of transcapsular rupture of the kidneys should hold the interest of every urologist because first, few have seen enough of them to develop a positive plan for their care, secondly, for guidance, one must rely upon the presentations of writers, whose personal experience is also limited, based on hospital records they have collected and reported facts to guide in the care of these unfortunate victims, and thirdly, tonight or tomorrow one might be faced with the problem of managing the case of such a victim of a fall, a blow, a collision, a crushing injury or even a brush with a stray or direct hit from a gun

Review of the literature on surgery for transcapsular rupture of the kidney reveals occasional reports of surgeons who have experienced a few cases Analyses of records of medical centers from coast to coast have appeared, which reveal their entire experience over many years with traumatic kidneys, however, the reports substantiate the impression that few surgeons have had large experience with the surgery of transcapsular rupture of the kidney

The reported experiences since 1940 of several groups have been studied for the occurrence of acute major injuries Listed in table 1 are the results of their medical and surgical treatment of cases so classified

It is significant that 1) early evaluations with retrograde pyelogram is favored as a routine by most writers, 2) among the nonsurgical cases, a) mortality is due largely to critically injured persons, b) morbidity is extremely high, and c) late sequelae indicating the need for surgery have a high rate among cases which have been followed, 3) among the surgical cases, nephrectomy, the usual operation, is followed by no morbidity and the mortality has declined from the 30 per cent plus of the previous decade to approximately 6 per cent in this series

The following reports of surgery for gunshot and shrapnel wounds among the Armed Forces have appeared For World War I by Hugh Young, 66 cases, for World War II in the Army by Kimbrough, 33 cases, in the Marines by Marshall, 24 cases, and in the European Theater, Robinson et al reported surgery for 63 cases of renal injuries, including 16 nephrectomies—47 conservative operations

It seemed desirable therefore, to prepare for publication the experience gained by one person over a span of 22 years in the treatment of 24 cases of transcapsular rupture of the kidney which came to surgery

Reference to lesser injuries, such as contusion, will not be made here Of the 24 patients, eight were shot Sixteen patients had no external wounds leading to the injured organ Of these subparietal traumas, seven came to prompt operation after immediate hospitalization, seven others were either hospitalized after

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Read before Section on Urology, meeting of American Medical Association, Atlantic City, N J June 10, 1955

TABLE 1. *Transcapsular ruptures selected from reported series*

	Orkin	Hodges, Gilbert Scott	Lynch	Mertz	McCague	Sargent and Marquart	Ferrier and King
Period covered	1940–48	1930–48	1940–47	1910–51	1929–49	1924–49	1933–41
Location	New York	Baltimore	Charlotte	Indianapolis	Pittsburgh	Milwaukee	Los Angeles
Total major injuries (probably transcapsular ruptures)	16	24	13	27	36	86	113
Attitude toward retrograde urography	Favorable	Favorable	Favorable	High favor	On indication	Favorable	Favorable
Nonsurgical cases							
Number	7	13	6	10	28	78	101
Morbidity rate.	30%	100%	16%	Considerable	?	13%	?
Sequelae for which surgery indicated	2	13		3	1	11	?
Mortality	2	0	1	5	5	6	37
Surgical Cases							
Number	9	11	7	17	8	8	12
Conservative surgery	4	6	3	7	6	0	?
Nephrectomy	5	5	4	10	2	8	?
Mortality	2	0	1	0	0	2	0

delay from 5 to 10 days; or were treated conservatively for varying periods before surgical intervention, the remaining 2 cases were considered spontaneous because their injury resulted from their own muscular force

During the waning years of the last decade, urologists were urged to abandon the common practice of palliating kidney injuries because late sequelae too often revealed such disasters as hypertension, infarcts, cysts, stones, infection and functionless organs Profound hematuria, recurrent hematuria, added infection and even masses were observed complacently until "hospital recovery." Many of these patients have been followed to their disabling sequelae A subsequent plea for conservative medical management has been heard

The purpose of this paper is to recommend a plan of early investigation of each case of renal trauma so that it may be classified for proper subsequent clinical care Preliminary care consists of treating the shock, and screening by excretory urography for evaluation of kidney damage If the urogram is clearly negative and no mass is present, and hematuria is declining to ceasing within 24 hours while the blood pressure is maintained, retrograde study can be deferred for several days The retrograde urogram, while indicated before the discharge of every patient with a trivial trauma, is at once mandatory when 1) the excretory urogram is not clearly negative, 2) there is a mass in the flank, 3) the hematuria persists or recurs after abatement, and 4) when infection intervenes Whenever urography demonstrates extravasation through the renal tissue into the renal fossa, a classification of transcapsular rupture is made Therapy, while always surgical in transcapsular rupture, can be planned to suit the general and specific conditions of the patient as immediate or deferred Prior care of associated injuries may at times be indicated Parenchymal ruptures producing hemorrhage into the renal fascia may not involve the lumen of the kidney and may yield only a mass In such cases exploration is indicated

Surgery may extend from simple drainage of the renal fossa, thorough removal of blood clots and degenerated fat, to apposition of the kidney laceration, partial, or total nephrectomy The first consideration is the life of the patient Successful conservation of the damaged kidney is gratifying to both the patient and the physician

Analysis of the series of 24 cases follows

Age and sex, side involved The age of the 24 patients extends from the proverbial 8 to 80 There were 19 males and 5 females The injury was shared equally by the right and left kidney, however, all the females were injured on the left

Trauma incident Of the eight who were shot, four received the bullet in the back and three from the front, the other received a full load of buckshot in the flank Among the subparietal group, the auto caused only three, two were passengers during a collision while the other was a pedestrian Falls produced ten injuries, down stairs, three, from bicyles, two, a window and a horse, one each, stumbled, three, one of these against a fire hydrant, one was crushed between the freight car which he was unloading into a truck when the brake slipped Without external violence, two ruptures were due to convulsive seizures as the rigors of vomiting in one and delirium tremens in the other

SYMPTOMS

Shock. Shock demands priority care and is of two types. The first is immediate, due to trauma itself and is characterized by lowered blood pressure, and slow pulse and respirations. The second type, caused by blood loss, presents a shift to a rapid pulse and respiration. The first state of shock is usually reversed spontaneously by the time the patient is hospitalized or soon after remedial

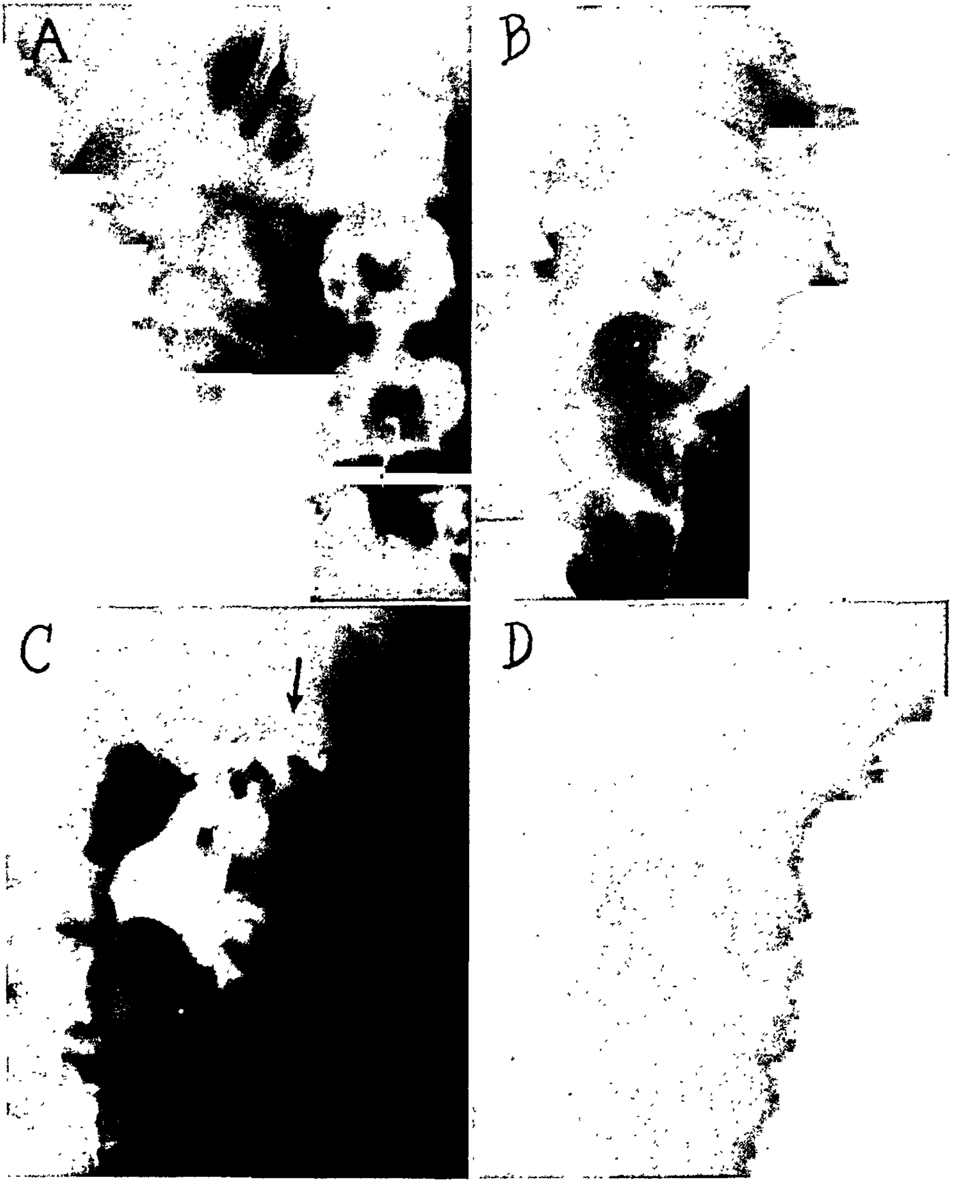

FIG. 1. *A*, case 5. Excretory urogram, delayed series, which is typical of perirenal extravasation of medium.

B, case 4. Retrograde pyelogram, immediate series, which is typical of extravasation through kidney lumen.

C and *D*, case 3, gunshot series. *C*, retrograde pyelogram reveals extravasation through upper pole into Gerota's fascia. *D*, retrograde pyelogram after postoperative drainage.

therapy is instituted When secondary shock occurs either by extension of the first or a relapse, keen clinical judgment will dictate the period of delay before surgical intervention In the presence of advancing hematoma and/or increase in abdominal hemorrhage from penetrating wounds, transfusion will sustain life to permit surgical intervention, in order that injured vessels may be ligated and viscera repaired Primary shock was present on admission in most of the cases which were admitted immediately after the injury The systolic pressure was less than 90 in 7 patients Shock responded to parenteral fluids and transfusion in most of the cases before abdominal exploration in the gunshot cases, in two of these, however, and in one of the subparietal injuries, surgery was launched before the systolic pressure had reached 100 The criterion of 100 + systolic pressure was met in each of the remaining cases

Hematuria Hematuria was present in every case sustaining external violence, and was recognized either upon voiding after the injury, or upon catheterization In the delayed series, there was recurrence of bleeding in 4 cases on the fourth, sixth, seventeenth and twentieth days respectively In only one of the spontaneous series, was there hematuria

Mass There was a painful, tender mass over the injured kidney in each of the subparietal cases upon admission In 4 patients who received immediate surgery, the mass was found to increase in size during the period of observation Both of the spontaneous cases presented masses but only one was painful

UROGRAPHY

Although retrograde urography has been utilized for more than half a century, it was not advocated as a part of the study of traumatic kidneys until after excretory urography had been tried and found wanting It is agreed that excretory urography performed after recovery from the shock is of value in accurately determining the state of the uninjured kidney In reported series where severe ruptures have been studied by excretory urography, and checked by retrograde urography and/or surgery, the rate of error has been enormous Fears shared by most early urologists of activating hemorrhage, or introducing infection have not been realized by those who have employed retrograde urography

Orkin's personal experience reported in 1950 revealed that only 13 of 32 excretory urograms were of satisfactory quality Of nine considered normal, four were proved to be transcapsular ruptures, three by retrograde study and one by surgery Another transcapsular rupture which was thought to be subcapsular was discovered by retrograde technique, and, of three interpreted as transcapsular ruptures, one was disproved and two were confirmed by retrograde urography Orkin used the gravity method in his twenty five retrograde pyelograms, all of which were satisfactory

Using excretory urography alone in 13 cases of this series, five presented positive impressions of transcapsular rupture which were confirmed by surgery, four appeared normal, but by retrograde study, transcapsular rupture was demonstrated, three failed to excrete on the injured side while a normal pattern was revealed on the opposite side, in the remaining case the suggestion of extrav

TABLE 2. *Gunshot series*

	Case 1 26 yr. male, S-1257 '36, 9/15/35	Case 2 35 yr. male, S-189 '36, 2/7/36	Case 3 26 yr. female, # 01-405, 8/9/36	Case 4 15 yr. female, #22-476, 2/26/46	Case 5 23 yr. male #51-179, 12/4/48	Case 6 34 yr. male, #82-480, 2/24/51	Case 7 41 yr. male, #57-319, 3/11/51	Case 8 23 yr. male, #93-776, 2/6/51
Interval to: hospitalization surgery discharge	1 hour 11 hours 39 days	½ hour 2 hours 21 days	½ hour 30 days 35 days	5 hours 27 days	½ hour 4 hours 11 days	½ hour 3 hours 10 days	2 hours 31 hours 71 days	15 min. 4 hours 7 days
Cause of injury	GSW of back; entered 2″ from midline in 10th ICS. Exit in 8th ICS on the right of MCL	Gunshot wound of back entered 4″ to right of midline at T 12. Bullet palpated 4″ from midline in 10th ICS anteriorly	GSW of neck, GSW of *abdomen*. *Entered* 4″ to left and 1″ above umbilicus. Exit just to the left of L 3	GSW of back entered just to left of T 12. Exit 4th ICS in ant. axillary line on same side.	Buckshot wound of *right flank* just below 10th rib	GSW of back. Entered 10th ICS *near* post. axillary line on left. No wound of exit	GSW of abdomen. *Entered epigastrium.* Exit through right flank just below costal margin	GWS of abdomen entered *right* hypochondrium. Exit right flank
Course before admission to urology service	Pain in chest when talking. Intoxicated	Sharp, severe pain in hypochondriac and epigastric region	Laparotomy performed 11 hours after injury. Spleen and omentum penetrated. Retroperitoneal hemorrhage noted	Patient in shock on admission. Laparotomy after 5 hours revealed penetration of cardia of stomach and tail of pancreas, 500 cc blood in peritoneal cavity	Laparotomy shortly after admission revealed injury to the liver alone. 525 cc fresh blood peritoneal cavity. Free pellets in abdomen	Laparotomy after control of shock revealed no damage of abdominal viscera	Laparotomy 2 hours after control of shock revealed penetration of liver and duodenum extraperitoneal hematoma in right renal fossa	Patient in severe shock on admission. Laparotomy revealed damage to right lobe of liver and evidence of rupture of kidney
State of shock	BP 71/00; pulse 60; temp. 98	BP 110/82, 10/68; temp. 91; pulse 60; resp. 30	BP 111/18, 62/10; temp. 101; resp. 101	BP 100/90; pulse 110; resp. 30	Pulse 98; BP 108/66, 100/72	BP 80/60; temp. 100.8; resp. 39; pulse 80	BP 100/80; pulse 96	BP 110/70; 80/50; pulse 110; resp. 28
Admission findings and clinical course	Muscles rigid over tender, dull kidney region and right abdomen	Rigidity, tenderness, and dullness over right flank and entire abdomen	Abdominal distention with *rigidity* and tenderness persisted over left kidney	Bloody vomitus	Tenderness over abdomen and right flank. Splinting. No vomiting	Pain in abdomen. Urgent desire to void and stool. Pain on respiration	Abdomen distended and tender. *Mass* in right flank and acute retention followed	Only complaint "*feeling cold*"
Urinary picture	Catheterized. Bright blood obtained	Bright red blood on catheterization	Catheterization. Gross hematuria. 16th—pyuria developed Frequency and urgency	Hematuria. Initially only	Gross hematuria with clots	Hematuria with clots	Grossly bloody urine	Catheterized urine very bloody
Blood picture	RBC 3.6; Hb. 65%			RBC 3.78; WBC 7.8; HC 25 (5th); HC 37 (31st)	RBC 4.65; HC 41; WBC 5	RBC 3.81; WBC 12.1; HC 49	HC 40; RBC 5.7	HC 41; WBC 15.6; HB 82%

Blood from right ureter Indigo excellent from left	None	Extravasation of medium through upper pole to renal fascia Normal right kidney	*D P 14th—Indecisive* D P 21st—Extravasation from upper pole of left kidney Right kidney normal	*None*	Bleeding from left side Right side normal I V extravasation from upper pole to perirenal area	Bleeding from right ureter I V a normal left kidney which could not be catheterized	I V not informatory on right Bloody urine from right Left O K
Penetrating wound of *the liver*	Penetrating wound of *the liver*	Patient 3 months pregnant on admission Penetrating wounds of neck and abdomen	Penetrating wound of stomach and pancreas	Penetrating wound of liver Fracture of 8th 9th and 10th ribs	Abdominal penetration bullet in midline in front of 2d L V body Damage to postlateral aspect of kidney	Penetrating wound of liver and duodenum	Laparotomy—penetrating liver
Laparotomy—1000 cc blood in right iliac fossa Stellate wound in liver sutured Right lumbar—many blood clots in Gerota s fascia Kidney placed in catgut basket	Laparotomy—1500 cc blood in abdomen Liver packed with gauze Left kidney palpated Right lumbar—hand full of clots Segment of kidney 1" cube free Nephrectomy	Clots within renal fascia Tear on posterolateral surface of kidney Two cigarette drains placed about injury	Kidney damaged at medial aspect 300 cc blood in renal fascia Penrose drains placed on both sides of upper pole	Numerous pellets penetrated to lateral border and anterior surface of kidney Nephrectomy *(transabdominal)*	50 cc dark blood in renal fascia Wound irrigated and penrose drain placed in	Massive blood clot and hemorrhage in renal fascia Kidney completely transected at junction of lower and *middle third* Bile stained peritoneum and colon	Parenchyma and pelvis completely bisected transversely Nephrectomy
Short period of shock *postop* Uneventful	Uneventful	Urinary fistula fol*lowed by healing*	Graceful	Uneventful	Stormy Persistent fever Suppuration in lesser peritoneal sac with sanguinous drainage on 15th day 2d operation by general surgery for drainage of abscess	Bile gastric and pancreatic juice, food and water flowed freely from kidney wound Digestion of mesentery of colon contributing to intraperitoneal hemorrhage and generalized hemorrhage Low nephron nephrosis occurred and recurred 3 secondary operations	Uneventful BP 100/60 after 5 hours of surgery
Indigo carmine appeared rt kidney 2 min Deep concentration	Recovery 65 days	Patients delivered full term normal infant	Recovery Returned to work on 29th P O day	Recovery	Recovery (spontaneous)	Died 76 days	Recovery

asation was confirmed by retrograde urogram. The only error among fourteen retrogrades studied was revealed when a repeat retrograde pyelogram disclosed extravasation. The comparative superiority of the retrograde over excretory urogram is overwhelmingly in favor of the former. Retrograde pyelography failed to revive hemorrhage in any case in this series. The introduction of infection could not be evaluated because surgery followed too closely (fig. 1).

ASSOCIATED INJURIES

All of the 8 patients who were shot were explored for visceral injuries. It was found that the liver had been injured 5 times, the liver alone in 4 patients, of whom one sustained fractures of the eighth, ninth, and tenth ribs on the right. In the remaining case, the descending loop of the duodenum was blown away. The stomach and pancreas, the spleen and omentum were involved in each of two others, while the remaining one had presented no penetration of abdominal viscera although the bullet was lodged in the lesser peritoneal cavity, which later became infected. *In one case a second bullet had penetrated the neck* of a pregnant woman. Among the subparietal cases, there were rib fractures in four. In the one who was pregnant, all ribs on the left and both ischial rami were fractured. The first four transverse processes of the lumbar vertebrae were fractured with separation of the third and fourth in one case; in another three ribs were fractured in addition to fracture of the right femur at its cervical neck with compound fractures of both the femur, in its lower third, and the right tibia, in its middle third.

SURGERY

The philosophy governing the surgery in this series was directed at intervention at the time after admission optimum, 1) to save the life of the patient; 2) to effect the most conservative surgery possible, and 3) to preserve function with the least possible morbidity. Surgery consisted of evacuation of free blood and urine, clots and disorganized fat from within the renal fascia, and drainage of the renal fossa with Penrose drains. In other cases the kidney lacerations were approximated directly when they were fresh and bleeding; when infarcted the area was removed and the kidney was repaired by either suturing the true capsule and/or binding the crushed kidney with figure of eight chromic catgut sutures. In the first case of the series, regular catgut was used but subsequently ribbon sutures were chosen. No partial nephrectomies were performed, but in accordance with present concepts this procedure would have been tenable in the first case of the series which was seen in 1932. Nephrectomy was performed only when the kidney was irreparably damaged or as a life saving measure.

Gunshot series. Laparotomy was performed on six of the gunshot patients within 1½, 2, 3, 4, 5, and 6 hours respectively; the other two were subjected to abdominal exploration at the tenth and fourteenth hour after the incident. Exploration at laparotomy disclosed hemorrhage in the kidney fossa in seven of the 8 patients. The condition of four of the patients was such that the urologic staff explored the kidney fossa through an extended flank incision to remove the kidney in two, repair it in one and drain the kidney fossa in another after evacuation of clots; the kidney was removed transperitoneally in the patient who got the full charge of buckshot in his left flank; the patient who lost the lateral margin of his duodenum underwent nephrectomy as a secondary operation 36 hours after the shooting; in the two female patients exploration of the kidney fossa, followed by removal of blood clots, lavage and drainage with Penrose drains occurred on the twenty-seventh and thirtieth days after the injury.

Three cases are briefly presented as follows (table 2):

GS-1: This man was admitted in profound shock within one hour and explored 11 hours later, when shock had improved notwithstanding the fact that the systolic pressure could not be raised above 90 with infusions of saline and glucose. A penetrated liver was the only evidence of visceral injury. A large mass of clots estimated to exceed 1000 cc was removed from the abdominal cavity. Many clots were removed from within Gerota's fascia. The kidney appeared like a "cracked nut" in its upper pole and presented numerous torn bleeding crevices. It was bandaged by figure of eight chromic catgut sutures Followup studies revealed complete functional restoration of the kidney.

GS-3: This young pregnant woman received gunshot wounds in the abdomen and neck. Within the hour at laparotomy, the damaged spleen and omentum were repaired; and hemorrhage was noted to be present about the left kidney. During the next 30 days of conservative therapy, hematuria and pyuria were

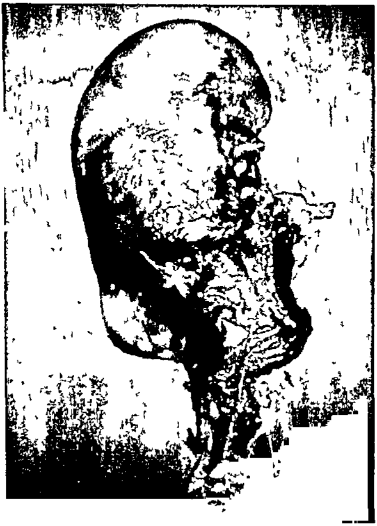

FIG 2 Case 7, gunshot series Kidney removed by nephrectomy with lower pole "blown away" by bullet which tore through descending limb of duodenum

TABLE 3. *Subparietal series; immediate group*

	Case 1 11 yr male, #16-35, 7/18/35	Case 2 47 yr. male, #01-458, 12/10/40	Case 3 19 yr. male, #6211, 1/30/44	Case 4 35 yr. male, #25-081, 6/26/46	Case 5 23 yr. female, #55-638, 4/11/49	Case 6 8 yr. male, #73-541, 7/3/50	Case 7 38 yr. female, #91-171, 12/15/51
Interval to: hospitalization surgery discharge	 3½ hours 2 days 18 days	 ½ hour 8½ hours 127 days	 6 hours 10 hours 19 days	 1 hour 26 hours 18 days	 4½ hours 20 hours 30 days	 8 hours 12 hours 8 days	 4 hours 90 minutes 9 days
Cause of injury	Fall from horse	Crushed between freight car and truck	Struck by automobile	Fell against water hydrant	Automobile collision	Fell down 12 concrete steps	Fell 15 ft. from window to pavement
Chief complaint	Hematuria. Pain in left side	Had extremely painful rt. side	Painful, tender right side	Painful left side	Painful left side from clavicle to ankle	Pain in right side	Painful right side
Course before hospitalization	Shortness of breath and vomiting were added	Unconsciousness had gradually developed	Unconsciousness for 5 hours. Had not voided	Hematuria, pain and swelling noted in left side	Short period of unconsciousness preceding painful left side	Walked home from scene, bent over, favoring right side	Hematuria. Carried into house; became unconscious
State of shock	BP 108/78; pulse 88; temp. 98; resp. 21	BP 60/0; pulse feeble and rapid; profound shock	BP 122/80; pulse 128	BP 115/60; pulse 60	BP 100/64; pulse 80	BP 96/60; pulse 92; mild shock	BP 90/60, 64/50; profound shock
Admission findings and clinical course	Painful, tender increasing mass in left flank Ileus	Painful, tender mass in left lumbar area enlarged rapidly. Vomiting	Painful, tender mass in right flank Abdominal distention	Painful, tender progressive mass in left flank Nausea and vomiting. Ileus developed.	Painful tenderness on left over ribs in back and pelvis in front. Mass in flank Pregnant (2 months)	Had not voided. Painful tender mass in splinted right flank	Painful, tender mass enlarging in splinted right flank
Urinary picture	Hematuria	Hematuria (bright red)	Gross hematuria and clots on catheterization	Hematuria	Hematuria with clots	Catheterized bloody urine with clots recovered	Hematuria with heavy clots
Blood picture	RBC 4.19; WBC 13.8	RBC 4.2; WBC 18.1; Serology +	RBC 2.70; WBC 11.6	RBC 3.6; WBC 1.9	RBC 3.31; WBC 8.3; HC 31; Hb 60%	RBC 3.8; WBC 5.8; HC 38 (a.m.); HC 29 (p.m.)	WBC 8.7; HC 40; Hb 14.1

Cystoscopy and pyelography	I V extravasation of medium through middle of parenchyma to perirenal area on left Right normal	I V novisualization on left Normal right kidney	Blood from right ureter D P extravasation about right kidney Left normal	Blood from left ureter D P Extravasation through parenchyma to perirenal area Right kidney normal	Clots in bladder D P Extravasation through parenchyma on left Right normal	Blood from right I V normal It suggested extravasation on right D P confirmed extravasation rt perirenal area	Blood from right D P Extravasation into renal fossa on right Left normal
Associated injuries		Fractures transverse processes of 1st 4 L V on left			On left, fracture all ribs and both ischial rami		Fractured ribs
Surgical findings and treatment	Many clots dark blood Kidney bisected Nephrectomy	Massive hematoma Bisected kidney Latissimus dorsi and psoas separated Nephrectomy Removal of fragments of vertebra	Massive hematoma Kidney bisected, lower third displaced Nephrectomy	Gerota s fascia filled with clots Gaping lacerations on anterior and lateral surfaces Nephrectomy	400 cc liquid blood and clots Contused muscles Upper third separated and displaced Nephrectomy	Renal fascia filled with clots and fresh blood Kidney transected Pedicle bleeding Nephrectomy	Hematoma Free bleeding Kidney transected with segments separated by clots
Postoperative course	Uneventful	Atelectasis, pneumonitis delayed healing of wound	Ileus was obstinate	Profound ileus, alcoholic, psychosis secondary wound healing	Uneventful	Uneventful	Uneventful
Follow up and results	Had developed normally	Full recovery and return to work in 8 months	Full recovery	Uneventful	Finished out school year Delivered normal baby in Oct '49	Normal development	Recovery

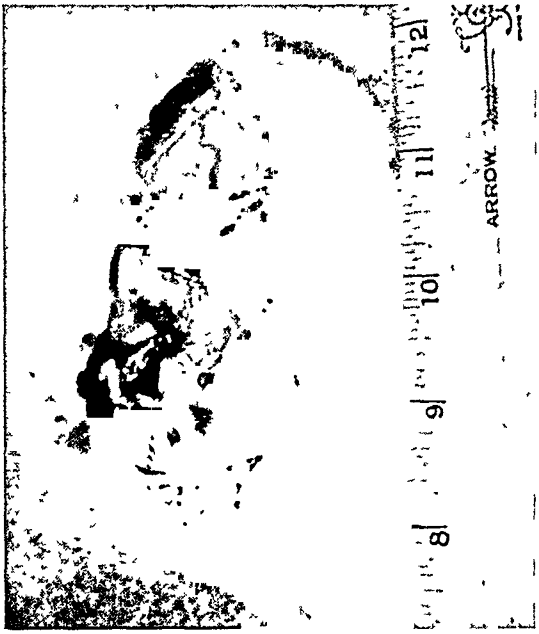

FIG. 3. Case 6, immediate series. Kidney removed by nephrectomy in 8-year-old boy who fell down twelve concrete steps.

striking features; pain in the left side was also present but no mass was ever palpated. Retrograde pyelography revealed extravasation into the renal fossa. When the clots were evacuated at surgery a tear was disclosed extending from the pelvis to the posterior lateral surface. Urine drained from the wound for 3 weeks. The kidney was proved to be normal both anatomically and functionally. She delivered a full term normal baby.

GS-7: This man received a bullet in his epigastrium which tore through the descending limb of the duodenum, the liver and the lower third of the right kidney. The immediate operation which consumed 3 hours effected repair of the duodenum and hemostasis of the liver wound. Nephrectomy was postponed until 34 hours after the shooting. Fistula followed breakdown of the duodenal repair and this initiated a series of untenable local and general conditions such as devitalization of tissue by escaping bile, and digestion of tissues by the pancreatic juices. The voluminous flow of the gastric juice over the wound encouraged infection, slough, hemorrhage, malnutrition, dehydration, hypoproteinemia, hypokalemia and many other complications. Three additional major surgical procedures were subsequently performed; one was complicated by lower nephron nephrosis, and followed by recovery from it. More than 300 laboratory studies were performed; dozens of quarts of blood and plasma were given and dozens of gallons of saline and glucose were administered. Death came seventy-six days after the injury (fig. 2).

Subparietal series. Immediate group: Surgery in this group was prompt after immediate hospitalization. It was performed within 2 to 12 hours in four of the 7 cases, and was delayed to 20, 24 and 27 hours in the other two. Nephrectomy was the only surgery performed, for the kidney was transected through the entire parenchyma in six and deeply lacerated into the pelvis in the other (table 3).

Three cases are outlined

I-2 This middle aged man was crushed between a freight car, which he was unloading, and a truck Upon immediate hospitalization, he was found to have a painful mass over the right kidney which increased in size, urine appeared as fresh blood During shock therapy, an excretory urogram revealed a normal left kidney but no visualization on the right Exploration revealed a kidney which was completely transected near its middle and bled freely once the perirenal fat and clots were removed Nephrectomy was performed The separated transverse processes of the second, third, and fourth vertebrae were removed His convalescence featured atelectasis and poor wound healing, more than four months of hospitalization, and about eight months for rehabilitation were required

I 5 This young pregnant woman was among a group of collegians whose auto crashed into a culvert, severely injuring all of five occupants Her injuries consisted of fractures of all of the ribs on the left as well as both ischial rami Shock followed a period of immediate unconsciousness A tender mass was present over the left kidney, at retrograde urography extravasation through the kidney was noted Exploration of the kidney fossa released about 400 cc of free blood and clots and revealed separation with displacement of the upper third of the organ The kidney was removed Convalescence was uneventful and the patient delivered her baby, normally, on time

I 6 This boy of eight, after falling down twelve concrete steps, walked home
bent over, favoring his painful right side When he was hospitalized 8 hours la
voided urine was very bloody, a painful mass over the right kidney was obser
to increase in size The hematocrit of 38 declined to 29 while his blood press
adjusted from 90/60 to 120/80 Excretory urography was suggestive of a
torted pattern on the affected side, but the direct pyelogram made under a
thesia, confirmed extravasation Continuing the anesthesia, the kidney
explored revealing much fresh blood and clots, the kidney had been bisected
the pedicle was bleeding, it was removed His convalescence was graceful
he was discharged on the eighth day (fig 3)

Delayed group Surgery in the delayed group preserved the injured kidne
2 cases Among the 4 patients who received late operations because their adr
sion was delayed to the fifth, sixth, tenth and eleventh days following
injury, three received nephrectomy, while the other received conservative rep
Another, whose associated injuries caused delay in definitive evaluation, recei
a nephrectomy for a severely lacerated kidney on the fourteenth day Two
tients were considered to have lesser injuries because hematuria became mi
scopic within 48 hours Their excretory urograms failed to suggest extravasati
there was no tender mass in the injured side early Later hematuria recurred,
flank became tender and a mass appeared urography revealed extravasati
The first case received a nephrectomy on the twenty eighth day, while the ot
received conservative repair of his injured kidney on the tenth day (table 4

D 2 This youth of 14 collided with a bicycle ridden by a playmate 6 d
before admission The impact occurred over the right upper abdomen, and
followed by a feeling of faintness, tenderness and vomiting Nausea and vomit

TABLE 4. *Subparietal series; delayed group*

	Case 1 16 yr. male, #49-408, 9/16/32	Case 2 14 yr. male, #07-572, 10/29/39	Case 3 15 yr. male, #06-784, 10/16/40	Case 4 80 yr. male, #19-792, 10/16/45	Case 5 21 yr. male, #27-488, 10/28/46	Case 6 29 yr. male, #29-930, 3/29/47	Case 7 29 yr. male, #38-495. 2/8/48
Interval to: hospitalization surgery discharge	 24 hours 28 days 29 days	 6 days 3 days 47 days	 5 days 3 days 20 days	 10 days 1 day 22 days	 11 days 7 hours 13 days	 20 hours 70 days 7 days	 2 hours 14 days 28 days
Cause of injury	Bicycle collision	Bicycle collision	Fall	Fall	Fall down stairs	Fall down stairs	Automobile collision
Chief complaint	Agonizing pain in left side. Bloody urine	Right quadrant pain; nausea; vomiting	Hematuria. Painful left side	Painful right side and flank	Clot retention. Pain and tenderness on left side	Hematuria. Painful right side	Sharp pain in chest and right side. Broken leg
Course before hospitalization	Walked home. Hospitalized next day.	Pain in right quadrant aggravated by voiding. Persistent vomiting	Dizziness. Shortness of breath for 5 days	Hematuria subsided 2d day. Occasional dark clots thereafter	Treated for rib fractures and discharged. Nausea and vomiting and hematuria persisted	Painful right side was worse. Hematuria	Sedated, wearing temporary splint for fractured femur. Adhesive strapping for rib fractures
State of shock	BP 175/105; pulse 120; resp 28; temp 101.6	BP 100/70; pulse 96; temp 101	BP 130/80; pulse 80	BP 135/80; pulse 65	BP 130/100	No shock; nausea or vomiting	Mild shock; BP 100/60; pulse 112; vomiting
Admission findings and Clinical course	Left flank tender, painful and rigid. Later: BP 122/72; rapid pulse; elevated temp; weakness	Hematuria. Painful, tender splinted right flank; no mass noted	Painful, tender mass; dizziness.	Painful, tender mass over right kidney	Painful, tender mass filling splinted right flank	Pain, tenderness gradually subsided Mass developed late as did ileus	Painful, tender mass right flank Hematuria
Urinary picture	Hematuria. 16th — Dysuria. 17th — Clot. Retention relieved. 28th — Severe hematuria	Hematuria was present, but not noticed	Gross hematuria persisted. Tenesmus developed.	One day of hematuria. Microscopic thereafter	Hematuria for one day. Recurred 4th day with tenesmus. 10th—clot retention.	48 hours of hematuria. Recurred 6th day. Pyuria developed late.	Hematuria gradually decreased. Recurred 12th day grossly

Blood picture	Later RBC 3 2, Hb 60%	RBC 4 22, WBC 22 2, Hb 70%	RBC 4 3, WBC 10, HC 40%	RBC 3 05, WBC 15, Hb 70%	RBC 4 46, WBC 8 75, Hb 70%	RBC 5 6 WBC 11 5, HC 53%	RBC 4 3 WBC 10, HC 10 Later RBC 2 8, WBC 6, HC 25
Cystoscopy and pyelography	Left hematuria Pyuria 18th I V Ureterectasis no filling, upper pole	I V and D P Extravasation through right kidney into renal fossa	D P Extravasation through kidney to perirenal area	Dark blood from right kidney D P Extravasation through kidney	I V Extravasation through kidney to perirenal area on left	I V normal on admission 9th day—right kidney, infected blood D P. Extravasation through lower pole to perirenal fossa	I V not definitive 14th day—D P Extravasation into renal fossa
Associated injuries	Lacerations of chest wall			Fracture of several ribs on right	Fractured ribs		Fractures Tr P all, Lt L vert, rt femur, cerv neck & comp, mid third right tibia comp
Surgical findings and treatment	Severely lacerated kidney Nephrectomy	Old clots free in renal fossa Figure 8 repair with tape catgut	Dark clots in renal fossa Numerous kidney lacerations extended into pelvis Nephrectomy	Dark clots infiltrating fat Deeply lacerated kidney with infarctions Nephrectomy	Dark clots in renal fossa Deep laceration Detached upper third Nephrectomy	Removed large organized clot posteriorly Ragged laceration in kidney. Edges freshened Area drained	Old clots Crushed kidney Nephrectomy
Postoperative course	Mild bronchopneumonia	Uneventful	Uneventful	Uneventful	Uneventful	Uneventful	Satisfactory
Follow up and results	Youth has developed normally No hypertension	I V on 30th postop day Excellent functionally and anatomically Normal developed adult	Has developed normally	Uneventful	Normal course	Cystoscopy after 3 weeks revealed equal function and normal anatomical pattern	Satisfactory

TABLE 5. *Subparietal series; spontaneous group*

	Case 1 34 yr. male, #02-119, 11/11/38	Case 2 56 yr. female. 1/28/40
Interval to:		
hospitalization		1 day
surgery	18 days	10 days
discharge	38 days	36 days
Cause of injury	Probably convulsion during hospitalization	Spasm of vomiting during G.I. upset
Chief complaint	Pain right side. Shock +	Mass in left upper hypochondrium just under rib margin
Course before hospitalization		Nausea, vomiting. Pain in epigastrium
State of shock	BP 130/90	
Admission findings and clinical course	Painful, tender mass right flank. Abdominal distention. Hematuria	Mass thought to be spleen. No tenderness or rigidity
Urinary picture	Hematuria	No hematuria
Blood picture		
Cystoscopy and pyelography	I.V. not informative D.P. visualized kidney lumen. Outlined lower pole of kidney mass. No extravasation	D.P. consistent with impression of parenchymal tumor of kidney
Associated injuries	None	None
Surgical findings and treatment	1500 cc clots removed from renal fascia. Deep laceration through ⅔ of parenchyma.	Approximately 1500 cc old and new clots in perirenal fascia. Lower pole of kidney "blown out."
Postoperative course	Uneventful. Discharged on 38th day.	Uneventful. Discharged on 36th day.
Followup and results	I.V. on 36th day revealed normal kidney.	L & W 12 yrs. P.O.

continued to his admission, while with subsidence of the flank pain, pain on urination occurred. There was fever on admission. An excretory urogram disclosed extravasation of medium through the lumen into the kidney fossa. Exploration of the right renal area revealed old blood and clots; there were two deep kidney lacerations, one with infarcted edges penetrated the pelvis in the lower pole, another more shallow one, with bleeding edges, was near the middle The infarcted edges were freshened and opposed, a figure of eight ribbon suture was used for the approximation The perirenal fat which was infiltrated with old blood clots was removed Convalescence was satisfactory for the period, and urography thirty nine days later revealed both function and architecture to be normal

D 4 This 80-year old man, after a fall, was treated for pain in his right side by adhesive straps over several fractured ribs Frank hematuria noted the first day was thereafter microscopic The persistence of a tender mass over the right kidney caused his referral for urologic study nine days after the injury An excretory urogram failed to show the injured kidney while the retrograde study disclosed bizarre puddling around the kidney Surgery revealed decomposed dark clots among the edematous, mottled, perirenal fat A deep laceration across the lower pole entered the pelvis of the spongy and swollen kidney Following the nephrectomy his convalescence was uneventful

D-7 This young man, brought to the hospital by an ambulance directly from the scene of an automobile collision, received care for his many right sided fractures of ribs, vertebra, femur and lower leg Hematuria and a tender right flank mass indicated urologic evaluation, excretory urography suggested conservative therapy for the kidney injury, as care for fractures proceeded Following recurrence of hematuria on the twelfth day, retrograde pyelography clearly showed extravasation of contrast medium through the kidney into the renal fossa, the tender mass appeared enlarged The hematocrit had shifted from 40 to 25 Surgery revealed old blood clots in the fossa, the kidney which was crushed at its upper pole and deeply lacerated through to the pelvis was removed The patient was returned to the fracture service after twenty eight days He was discharged as recovered after four months

Spontaneous group The 2 cases classified as spontaneous are both unique for each was incident to rigorous muscular spasm The kidneys were severely torn and massive hematomas were found within the renal fascia There was delay in establishing a diagnosis in each case (table 5)

S 1 One, a man, was a known alcoholic, subject to convulsive delirium tremens He was found unconscious in the bathroom and upon being revived visited his family physician who caused him to be admitted to the medical service The next day a severe convulsion was followed by a state of unconsciousness During the state of relaxation which followed, it was noted that the urine and stool mixture found in his bed was bloody A week elapsed before the urologic service was called Study revealed that a tender mass appeared in the right flank the day following his convulsion in the hospital, and that the urine itself was never noted to be grossly bloody though microscopic blood persisted Neither excretory urography on the eighth, nor retrograde pyelography on the eleventh day revealed urinary extravasation, an outline of the shadow of the renal fascia, however, suggested an enlarging mass within Surgery on the eighteenth day revealed a volume of old blood, clots and disorganized perirenal fat estimated to be 1500 cc within the renal fascia, which bulged below the iliac crest A jagged

FIG. 4. Case 2, spontaneous series Retrograde pyelogram No extravasation noted. Bizarre pyelogram in presence of mass suggested tumor.

FIG. 5. Case 2, spontaneous series Kidney removed by nephrectomy reveals "blowout" of lower pole. Massive clots found within Gerota's fascia.

tear to, but not into the pelvis extended two-thirds around the kidney circumference at the junction of its middle and lower third It was repaired by figure of eight ribbon suture

The followup study revealed excellent function but the anatomic pattern of the middle calyceal group was indistinct

S 2· This short, stout 56 year old school teacher came to the attention of her physician after a severe bout of vomiting After relief during the night, examination the next morning revealed a tender mass suggestive of the spleen in the upper quadrant Although there was no hematuria, an excretory urogram disclosed no function on the left, the retrograde pyelogram suggested parenchymal tumor Exposure of the kidney fossa disclosed a mass of old blood, and clots among the perirenal fat and a "blowout" of the lower pole of the kidney Nephrectomy was followed by uneventful convalescence She has enjoyed excellent health during the intervening 15 years (figs 4 and 5)

TABLE 6 *Surgery*

Groups	No of Cases	Nephrectomy	Conservative
Gunshot	8	1*	4
Subparietal			
Immediate	7	7	
Delayed	7	5	2
Spontaneous	2	1	1
Total	24	17	7

* Only death 76 days after a shot tore away duodenum and lower pole of kidney

RESULTS

A total of 24 patients treated surgically for transcapsular rupture of the kidney have been listed in the foregoing groups, as outlined Of this number seventeen were nephrectomized and seven received conservative surgery Sixteen of the seventeen nephrectomized patients have lived normal lives and the other nephrectomized patient died 76 days after being shot, from a series of complications which were initiated by a tear in the duodenum The seven who received conservative surgery are known to have returned to productive life, of the five whose kidneys were studied after surgery, all presented evidence of satisfactory function without infection The pyelogram of one, however, did not appear normal in the area of the middle calyx which was the site of injury (table 6)

CONCLUSION

In conclusion, the following formula for management of ruptured kidneys is offered

Following an injury where hematuria is found, after control of shock (if present) attention should be directed toward complete investigation of the anatomic configuration of the kidney

Excretory urography may be employed when shock has been controlled If a pyelographic pattern consistent with normal is not clearly apparent, a retrograde pyelogram must promptly be effected.

Retrograde urography should be instituted before the discharge of every kidney injury.

If the lumen of the kidney is violated, plans for surgical intervention should be made.

The presence of an enlarging mass in the flank warrants the application of emergency surgical measures after knowledge of the other kidney is obtained. Early consultation with the service responsible for the care of the associated injuries found in these patients will result in more satisfactory recovery and few untoward sequelae.

When hematuria is intense and continuously prolonged, emergency surgery is tenable after knowledge of the other kidney is obtained.

Recurrence of frank hematuria is cause for re-evaluation, for this may cause a shift from the conservative plan of therapy.

In the absence of an increasing mass in the flank, surgery, when temporarily deferred, permits the subsidence of active hemorrhage and provides at surgery for a more satisfactory evaluation of the local injury; thus yielding the maximum number of conservative repairs.

High tribute is paid to the referring surgical service which received many of these patients and immediately launched shock therapy, and in the gunshot cases, emergency laparotomy.

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CONCOMITANT INTRARENAL AND PARARENAL ANGIOMYOLIPOMAS*

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Lipomatous tumors of the retroperitoneal tissues are not uncommon[1, 2] The majority, according to Mayo and Dixon,[3] occur between the lower pole of the kidney and the pelvic brim Ackerman[4] states " They have a predilection for the pararenal area Their intimate relation to the kidney may necessitate its removal " Intrarenal lipomas, of sufficient size to be of clinical significance, are rare Approximately forty cases, not including the so called "capsulomas,"[5] have been reported [6] Some have been pure lipomas, about half have had intermixed other components, and have been called fibrolipoma, angiomyolipoma, hamartoma, etc We have been unable to find a report of concomitant occurrence of renal and pararenal lipoma The following case is of interest in that it demonstrates not only the occurrence of lipomatous tumors, both within and in the vicinity of the kidney, but also the recurrence of a pararenal tumor more than ten years after the original resection

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* This case was demonstrated at the Slide Seminar during the ninth Annual Tumor Day, November 1954, at the Albert Einstein Medical Center, Dr N C Foot (Cornell University Medical College) moderator

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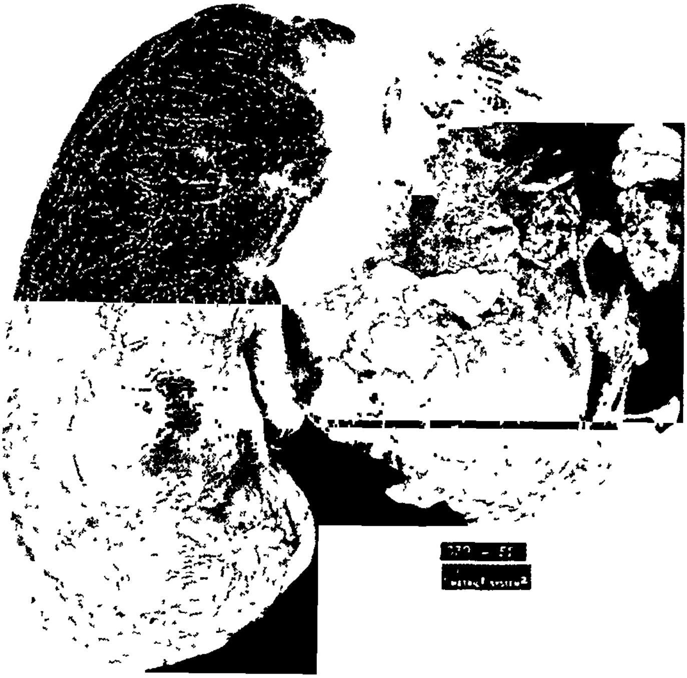

FIG. 1. On left is bean-shaped pararenal lipomatous mass. On right is kidney showing fatty masses protruding both medially and laterally from lower half of kidney.

CASE REPORT

In October 1941, a 29-year-old woman, because of abdominal symptoms, was surgically explored at another hospital. A large fatty tumor was removed from the vicinity of the lower pole of the left kidney. The pathological diagnosis was retroperitoneal leiomyolipoma. The patient was in good health and asymptomatic, for the following 10 years. In this period, she had two uneventful pregnancies. In February 1952, during a routine gynecologic checkup, a large abdominal mass was palpated. Gastrointestinal studies were negative. Excretory

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urography demonstrated a "space-taking lesion," with distortion of the inferior and middle calyces of the left kidney. Below the left kidney was a second large soft tissue mass, its translucency suggesting lipid. A gynecologic consultant found, in addition, an enlarged, myomatous uterus.

A left retroperitoneal exploration, through a left lumbar incision, was carried out on February 26, 1952. When the left kidney was explored, a large, oval, orange, fatty mass was found involving the lower pole, extending into the hilus. Nearby were several smaller, similar nodules. When the kidney was removed, a large retroperitoneal tumor of similar consistency was found. The postoperative course was uneventful. In the three years since operation, there has been no evidence of recurrence. The patient has no demonstrable lipomas. She shows none of the external components of the tuberous sclerosis complex.

The surgical specimen (figs. 1 and 2) consisted of two portions. One was the left kidney, measuring 12 by 5 by 4 cm. The lower pole was enlarged, a number of lipomatous protrusions increased its dimensions to 8 cm. transversely and 5 cm. anteroposteriorly. A segment of attached ureter was displaced posteriorly. The renal pelvis was extrarenal, and subdivided into three trunks, connected with three separate calyces, which were not distended. On longitudinal section, about one-third of the lower half of the kidney was replaced by fatty masses. The largest of these, continuous with the largest protruding mass, measured approximately 7 by 5 cm. on its cut surface. Numbers of smaller fatty nodules, apparently discrete, were found scattered through the lower half of the kidney. The masses were without distinct lobulation, and had an orange yellow color. The large, separately removed tumor measured 17 by 7 by 5 cm., was bean-shaped, with most of its surface smooth and encapsulated. The fat had a somewhat orange cast, its cut surface was indistinctly lobulated, varying from yellowish to orange yellow. On microscopic study (fig. 3, *A*, *B*, *C*) the pararenal and

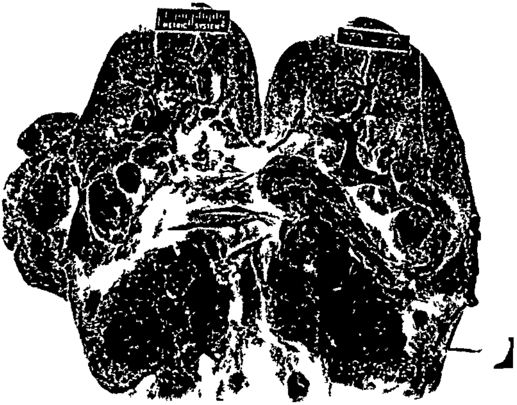

FIG. 2. Bisected kidney showing fatty tumor masses in lower half of kidney.

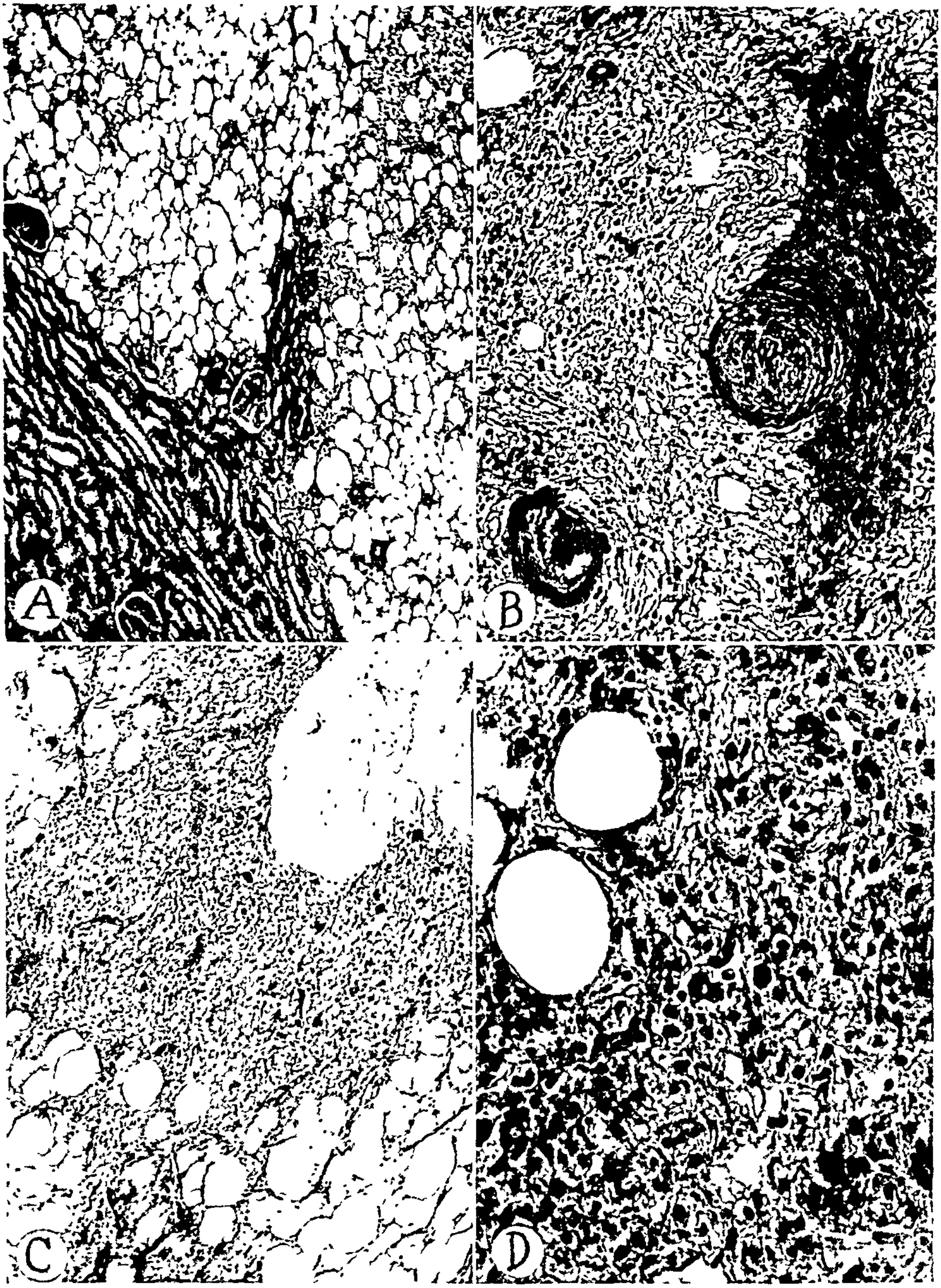

FIG. 3. *A*, section from kidney showing adult adipose tissue separating renal parenchyma. *B*, showing smooth muscle related to a thick-walled blood vessel. *C*, small focus showing some degree of anaplasia in otherwise mature lipoma. *D*, focus of frank sarcoma in a retroperitoneal lipoma.

intrarenal tumors showed the same histological pictures. Mature adipose tissue formed the greatest part of the tumors. In the kidney, the tumor extended between and separated the normal renal elements. Scattered through the tumor were small foci of spindle-shaped cells, having the appearance and staining qualities of smooth muscle, and associated with blood vessels In the pararenal tumor, one small focus showed some cellular irregularity, with occasional large nuclei The diagnosis was intrarenal and pararenal angiomyolipomas

A number of questions are raised by this case The first problem concerns the relation of the tumor removed in 1941 to those found in 1952 The histological appearance of the original tumor, and of the recurrence, was that of a benign tumor Farbman[1] in his review of retroperitoneal fatty tumors, wrote "there have been cases recorded in which recurrent tumors have been removed five or six times " Windholz (his case 1)[7] reported the recurrence of multiple retroperitoneal lipomas 1½ years after the original removal There was no further followup Ockuly and Douglas[8] refer, without specific citation, to cases of recurrence, in which two or three subsequent removals were necessary Pertinent is the report by De Weerd and Dockerty[9] that two patients with benign retroperitoneal lipoma ultimately succumbed to recurrent tumor more than 10 years after original complete removal In our case, the more recent tumors were histologically similar to the original tumor It is unlikely that the tumors, in the form found at the second operation, were present at the initial exploration It is also unlikely that the small anaplastic focus in the recurrent tumor is necessary proof of malignancy Liposarcoma usually arises as liposarcoma, *ab initio*[9] There have been a few reports, however, of liposarcomatous change in benign lipoma[10, 11] One of us recently saw a small focus of liposarcoma in a histologically benign appearing retroperitoneal lipoma which accompanied a separate typical retroperitoneal liposarcoma In that case, the histological evidence of malignancy in the small central focus was clear (fig *3, D*)

It is unlikely that a large intrarenal lipoma was present in 1941, there might have been, at that time, a very small tumor The intrarenal tumor was completely separate from the pararenal tumor, though the two were practically identical histologically Multiple lipomas are not infrequent, they may be synchronous or metachronous Tedeschi[12] has reported a case of apparently benign lipomas with multiple "metastases" and fatal outcome

Primary liposarcoma of the kidney has been even less frequently reported than intrarenal lipoma Of considerable interest is the high degree of association of tuberous sclerosis with liposarcoma of the kidney[13, 14] Our patient gives no evidence of tuberous sclerosis

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Three years have passed since the nephrectomy. There is no evidence of recurrence. More than ten years separated the first and second operations. It is not possible to be certain that there will be no further recurrence. This would be so even if the small cellular focus had not been demonstrated. In the series of forty retroperitoneal and two intrarenal lipomatous tumors reported from the Mayo Clinic in 1933 by Pemberton and McCaughan[6-t] there were 12 cases with recurrence; six of these were in cases which had originally been considered benign. It is of interest that 1 case was operated upon 4 times, and 1 case 3 times, for recurrence. In the more recent report from the Mayo Clinic by De Weerd and Dockerty[2] they mention 1 case of benign lipomatous retroperitoneal tumor in which recurrence occurred 5 years after operation. Another of their cases with a benign retroperitoneal tumor had two subsequent operations for recurrent tumor, and died four years after the initial operation. Another, alive after 10 years, had "extensive incapacitating recurrence." Still another died 18 years later with a retroperitoneal lipofibrosarcoma. In Farbman's review[1] of retroperitoneal fatty tumors reported between 1937 and 1947, he states that six of the fourteen benign tumors in which there were followup records showed recurrence, and three of these were sarcomatous.

Only time will tell if cure has been obtained. There is little indication that irradiation is of any value,[1, 2] although Stout[9] has suggested that this mode of therapy should not be abandoned.

SUMMARY

A case of intrarenal and pararenal lipomas is reported, in which the pararenal tumor represents a recurrence more than 10 years following primary resection.

We wish to thank Dr. Charles Maser who performed the original surgery for the clinical records concerning the original operation and Dr. David Meranze for the opportunity of studying the slides of the original tumor, removed at the then Mount Sinai Hospital, Philadelphia. We also wish to thank Mr. Joseph Poppel, Jefferson Medical College, for the taking of the photomicrographs.

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THE UNSUITABILITY OF POLYVINYL PLASTIC FOR URETERAL SPLINTING

DAVID M DAVIS

In 1947 the Resident in Urology at the Jefferson Hospital performed the operation of intubated ureterotomy, using a polyvinyl tube as a splint. The tube remained in place 4 weeks The ureter became occluded, and nephrectomy was necessary.

A year or two later a colleague in Philadelphia performed a similar operation, also using a polyvinyl tube, with the same result

Judging from these experiences, I was not sure that the bad results were due to the polyvinyl plastic, but nevertheless refrained from using it, and obtained uniformly good results with rubber tubing

Recently I saw a patient from another state who had undergone intubated ureterotomy operations, first on the right side and then on the left. Following these operations urine came through the ureters for only a day or two, and it was necessary to maintain nephrostomy drainage Polyvinyl splinting tubes were used on both sides, and left in place 6 weeks

Seven months after the operation on the right side, and 4 months after the operation on the left side catheters ascended each side for only about 3 or 4 cm , and no fluid could be forced through either ureter in either direction Injection of radiopaque solution through the nephrostomy tubes showed that there was no lumen whatever in the upper ureter on either side

During an operation to provide substitute ureters, which will be fully described in a subsequent publication, a section of the lower and middle portions of the right ureter about five inches long was removed for study. The accompanying photomicrographs (fig 1) show how the ureter was occluded by what looks like a deposition of submucosal scar tissue, with perhaps the addition of an overgrowth of smooth muscle, although a tiny nest of epithelial cells remains at the center

Polyvinyl tubing has been recommended by a few operators for ureteral splinting, so one must assume that it does not always produce bad results Probably the bad results occur in patients who have an individual sensitivity to the plastic base or to the plasticizing substance used in polyvinyl tubing

The extremely serious—even tragic—results of ureteral occlusion induce me to urge all surgeons as emphatically as I can not to use polyvinyl tubing for ureteral splinting There is no occasion for taking the risk involved since good quality red rubber tubing is entirely satisfactory, and does not cause occlusion

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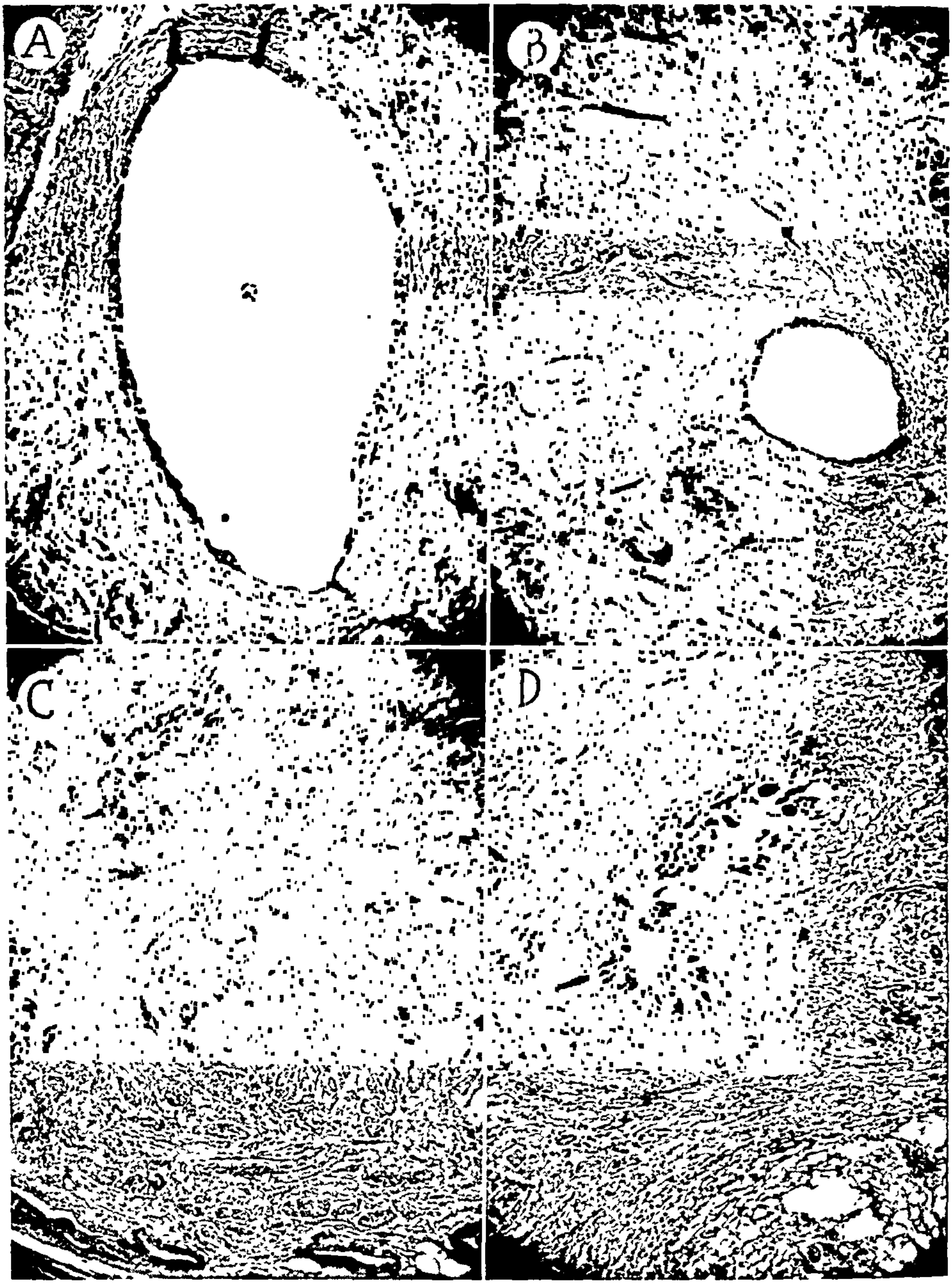

Fig. 1. *A*, low power photomicrograph of juxtavesical portion of right ureter, where lumen is of almost normal dimensions. *B*, low power. Mid-pelvic portion of the right ureter, showing reduced lumen and much scarring between epithelium and muscular coat. *C*, low power. Section taken just above level of iliac artery. Practically complete obliteration of lumen. Muscle bundles seem to be growing into scar tissue. Small island of epithelium surviving. *D*, high power. Same section as *C*, showing surviving island of epithelium.

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DELAYED CYSTOGRAPHY AND VOIDING CYSTOURETEROGRAPHY

CHARLES MONTGOMERY STEWART

When opaque media are instilled into the urinary bladder and retained continuously while x-ray exposures are obtained at variable intervals during the next one to three hours, the resultant film studies have been termed "delayed cystograms."

With contrast media retained in the bladder of patients in whom ureteral reflux has been proved or suspected, x-ray exposures are obtained with the patient in the erect position during the act of voiding and this diagnostic technique has been termed "voiding cystoureterography."

Previous to the use of delayed cystography, it was assumed that ureteral reflux either occurred immediately or not at all. It is now known that reflux may be delayed for any time interval, from several minutes to several hours. Ureteral reflux may be immediate, delayed, recurrent, unilateral, alternating unilateral or bilateral when x-ray exposures of the contrast medium-filled bladder are made at 15 minute intervals during a 1 to 3 hour period. If vesicoureteral reflux does occur during a delayed cystographic study, it may also occur during the act of voiding. In some patients reflux may be evident during delayed cystography and it will not occur with voiding. Reflux has been proven to occur only during micturition in a few patients.

DEFINITION AND TECHNIQUE

Instillation is accomplished through a catheter using a piston or bulb syringe. The bladder need not be over distended. Reflux may occur with the bladder only partially filled. The amount of medium instilled is variable and must be estimated according to the patient's age, ability to co-operate, and the degree of evident vesical irritability. One to four ounces are usually sufficient for infants and children. The quantity necessary for the average adult may vary from four to ten ounces. *Over distension is not necessary!* Best results are usually obtained when the bladder is filled only to a degree compatible with comfort.

Instill the solution slowly, preferably using a slightly warmed contrast medium.

In children and adult females of nervous temperament, a preliminary competent local urethral anesthetic is recommended. Local anesthesia partially masks the sensation of urgency often resulting from passage of a catheter as well as reducing the chemical irritation common in some degree to all cystographic contrast media.

Of four types of contrast media used during the past 7 years, urokon has been proved to cause the least chemical urgency when retained in the bladder for 2

Read at the annual meeting of the American Urological Association in Los Angeles, California, May 19, 1955.

Note by editor: Doctor Stewart's exhibit was awarded first prize in the Division of Clinical Research by the Committee to Judge Scientific Exhibits. Dr. William M. Coppridge, chairman.

to 3-hour intervals. Urokon in concentrations of 18–20 per cent is recommended. This concentration is necessary in the detection of a beginning reflux in patients in whom the medium is diluted as it enters a dilated ureter.

In infants and children too young or too ill to co-operate, instillation should be done through a 5 cc Foley retention catheter of small caliber. The contrast medium may then be retained in the bladder for any desired time interval by use of a catheter clamp.

Films are exposed immediately following the instillation and at 15 to 30-minute intervals thereafter. Reflux has been delayed in some instances as long as two and one-half to three hours. Reflux may occur at one interval and disappear at a later interval. For this reason each film should be developed and viewed immediately. The time intervals and variations in angle of exposure can then be changed to supplement the immediate x-ray findings.

Voiding cystoureterographic studies may be made at the termination of a delayed cystographic series, or they may be made immediately following the bladder instillation of contrast medium. Simply stand the patient erect and take the film exposures while the patient is voiding as forcibly as possible.

In infants and children too young to co-operate, the bladder may be slightly overfilled, the catheter removed, and with the patient supine or partially erect, a film should be taken as soon as the child strains to void.

VOIDING CYSTOURETEROGRAPHY

During the past 2½ years, voiding cystoureterographic studies have recorded some phenomenal vesicoureteral reflux antics which were previously unsuspected. In patients having proven ureteral reflux by delayed cystography, films should be taken with the patient erect and forcibly voiding. When voiding reflux does occur, the amount of reflux and the degree of upper urinary tract dilatation demonstrated are usually far greater than that demonstrated by non-voiding cystography.

Two and one-half years ago the possibility of a voiding reflux was first suspected and proved in a 6-year old girl. The child had a congenital bladder neck obstruction corrected by transurethral resection at 18 months of age. Residual urine of 60 cc was reduced to zero. During her initial urological workup, delayed recurrent ureteral reflux was demonstrated on 15-minute interval x-ray exposures taken during a 2-hour delayed cystogram study. In spite of the absence of residual urine, pyuria continued to be recurrent. Residual urine gradually recurred by her fourth year of age. A second transurethral resection during her fourth year again reduced a 2-ounce residual urine to zero. Pyuria continued to be recurrent but symptomless. Repeated checks for residual urine revealed no bladder retention.

In October 1952, approximately eighteen months after her second resection, it was suspected that a portion of the bladder urine might reflux into one or both kidneys during the act of voiding. A 2-hour delayed cystographic study was made, taking x-ray exposures at 15-minute intervals, and this study revealed recurrent unilateral and bilateral complete and partial reflux during this 2-hour

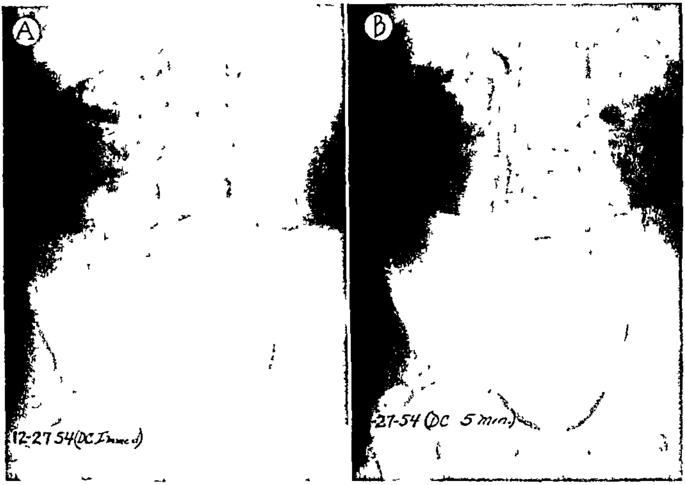


Fig 1. Case of D. H., a boy aged 13 years. Recurrent chills, fever, and severe pyuria since birth. No residual urine. Patient voided prompt, forceful stream. Repeated cystourethroscopic examinations revealed no obstruction at bladder neck, no trabeculation. Ureteral orifices visually competent, jets forceful. Repeated excretory urograms and retrograde pyelo-ureterograms revealed no gross abnormality.

A and *B*, delayed cystographic studies following instillation of 300 cc 20 per cent urokon into bladder through catheter. *A*, immediate film. *B*, 5-minute film.

period. With the contrast medium still retained in the bladder, the child was placed in the erect position and x-rays were taken during the act of voiding. Our suspicion was verified: The child had voided bilaterally into both ureters and kidneys. This accounted for the absence of residual urine when a catheter was passed immediately after voiding. However, if approximately 2 minutes were allowed to elapse between voiding and passage of the catheter, it was found that 40 to 60 cc of urine were obtained. This residual urine had been voided retrograde into the upper urinary tract, returning to the bladder within a two-minute interval following voiding. This has been termed a delayed check for voiding reflux residual urine. This child's voiding reflux undoubtedly was responsible for her recurrent pyuria.

Voiding reflux has since been suspected and demonstrated in a rather large number of children and in several adult females. Each of these patients suffers from recurrent or persistent pyuria and although neurogenic and/or mechanical obstruction is undoubtedly the initiating cause of the voiding reflux and resultant infection, an actual pathological lesion has not been demonstrated in all of these patients.

For example, voiding reflux was evident in a boy aged 13 (figs. 1, 2 and 3) and a girl aged 8 (figs. 4, 5 and 6) selected from this series. Each child has a lifelong

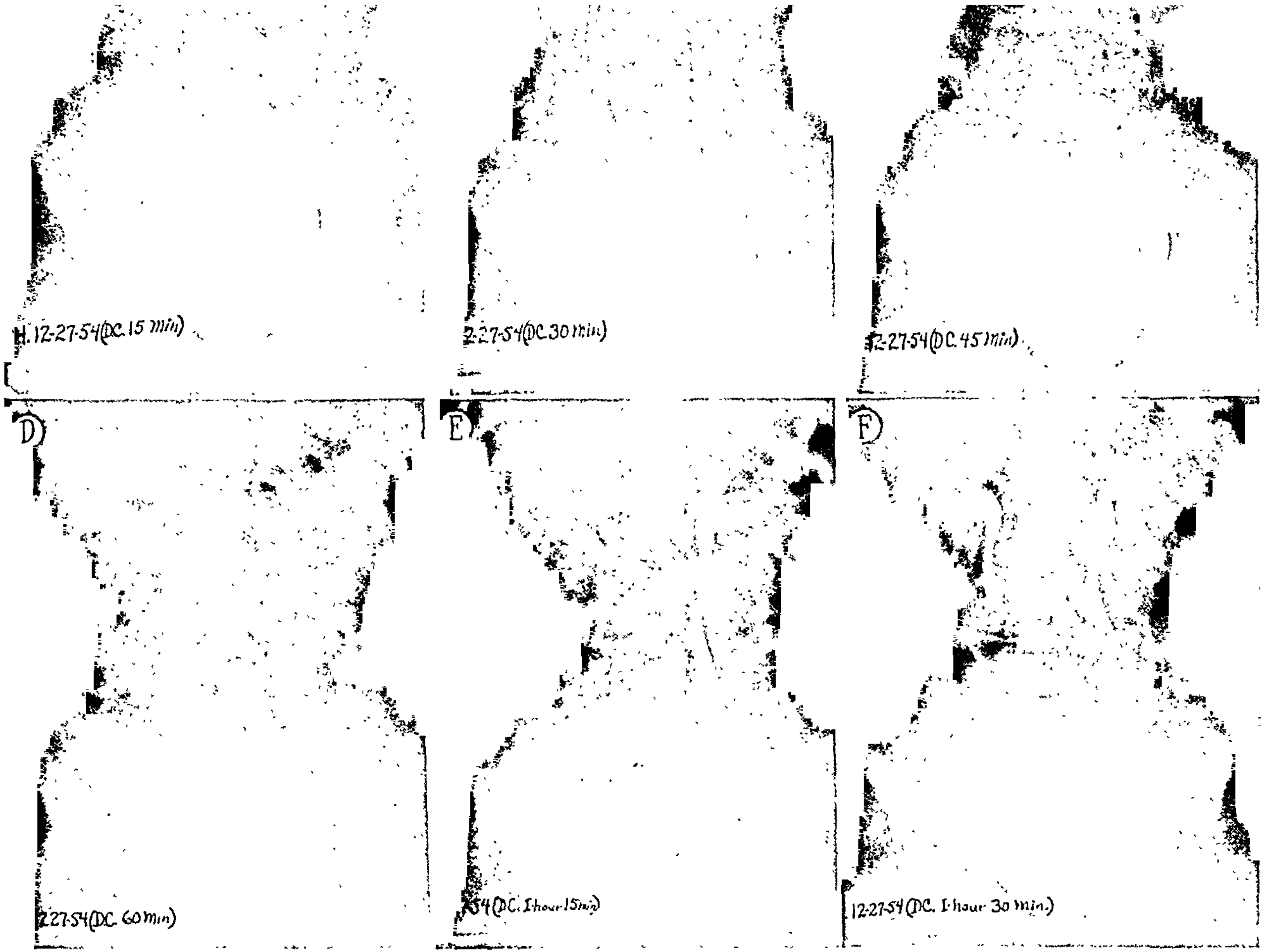


FIG. 2. Same case as figure 1. Delayed cystographic studies. Exposures taken at 15 minutes and at 15 minute intervals thereafter for 1 hour and 30 minutes. These exposures made with patient in supine position. Vesicoureteral reflux is bilateral and recurrent during 90-minute period.

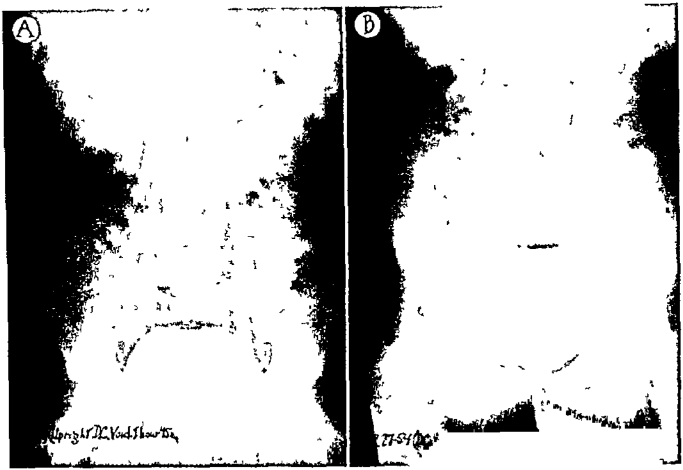


FIG. 3. Same case as figures 1 and 2. Delayed cystographic studies. Film exposures with patient in upright position while forcibly voiding at 1 hour, 45 minutes and 2 hours respectively Renal and ureteral dilatation demonstrated during micturition is severe.

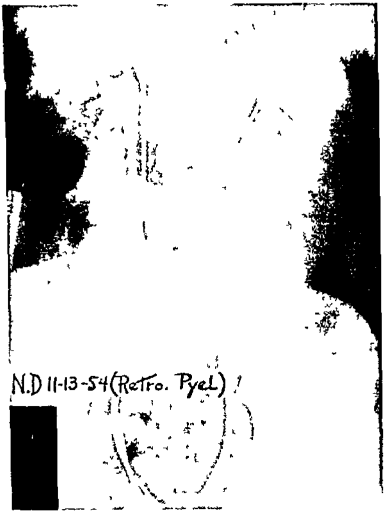


FIG 4. Case of N. D , a girl aged 8 years. Recurrent pyuria, chills, fever and occasional attack of aching pain in right upper abdomen. Patient had always had prompt, continuous, forceful urinary stream No residual urine. Repeated excretory urograms and retrograde pyeloureterograms revealed no pathological process on left side and a double fused kidney with complete duplication of ureters on right. Right lower component revealed some evidence of pyelonephritis on several occasions but no gross evidence of ureteral or renal dilatation

Retrograde pyelograms with catheters in place.

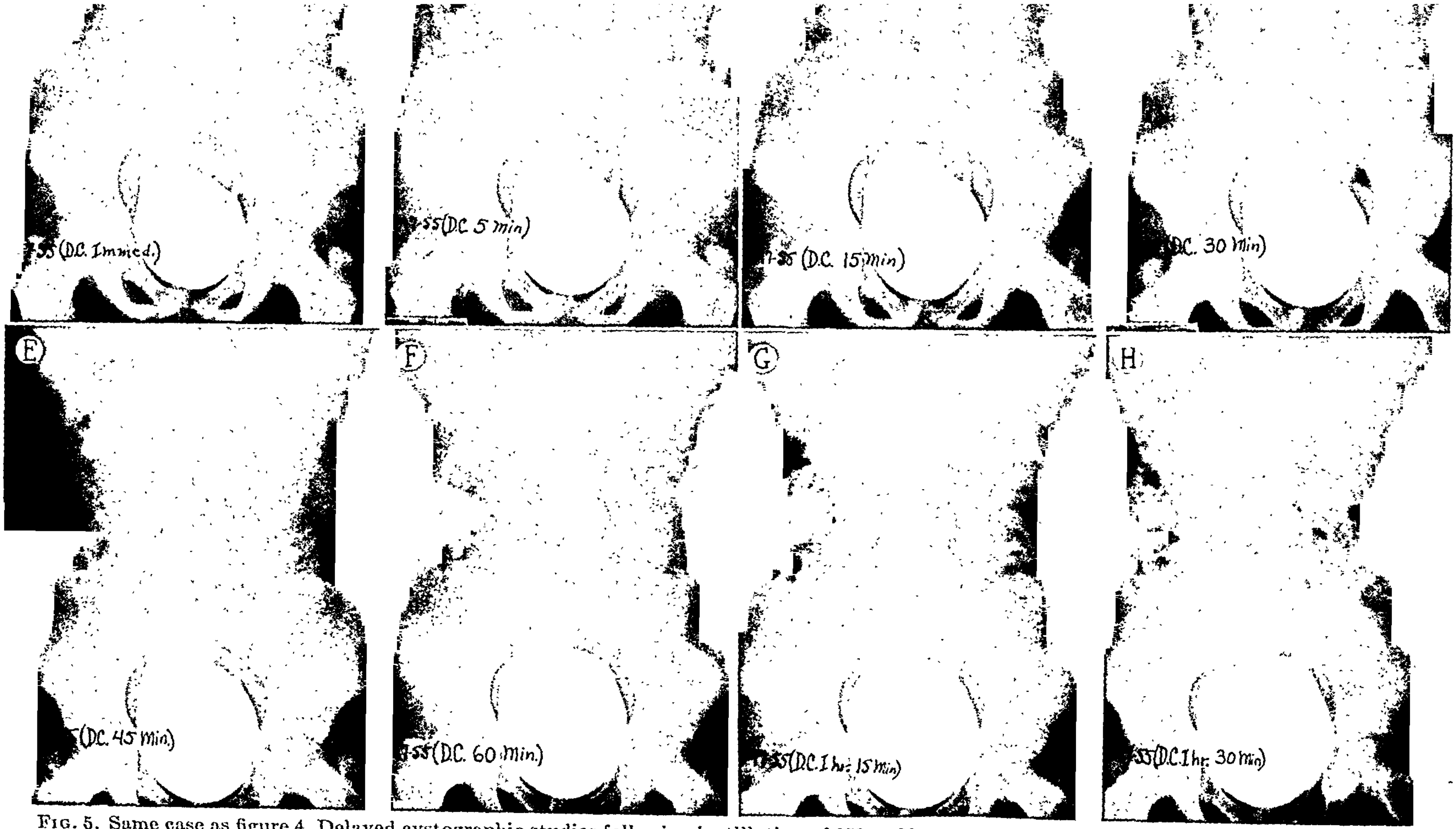


FIG. 5. Same case as figure 4. Delayed cystographic studies following instillation of 250 cc 20 per cent urokon into bladder. *A*, immediate exposure. *B*, exposure taken 5 minutes after instillation of medium. *C*, *D*, *E*, *F*, *G* and *H*, films taken in supine position at 15-minute intervals for 1½ hours. Reflux evident into lower component on right side and partial reflux filling on left side.

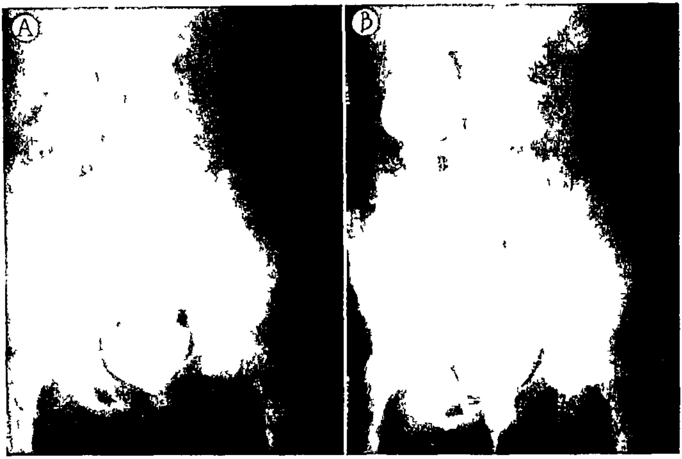


FIG 6 Same case as figures 4 and 5 Exposures taken at 1 hour, 30 minutes and 1 hour, 40 minutes with patient in erect position and while voiding forcibly Degree of upper tract damage demonstrated by voiding cystourethrography is apparent

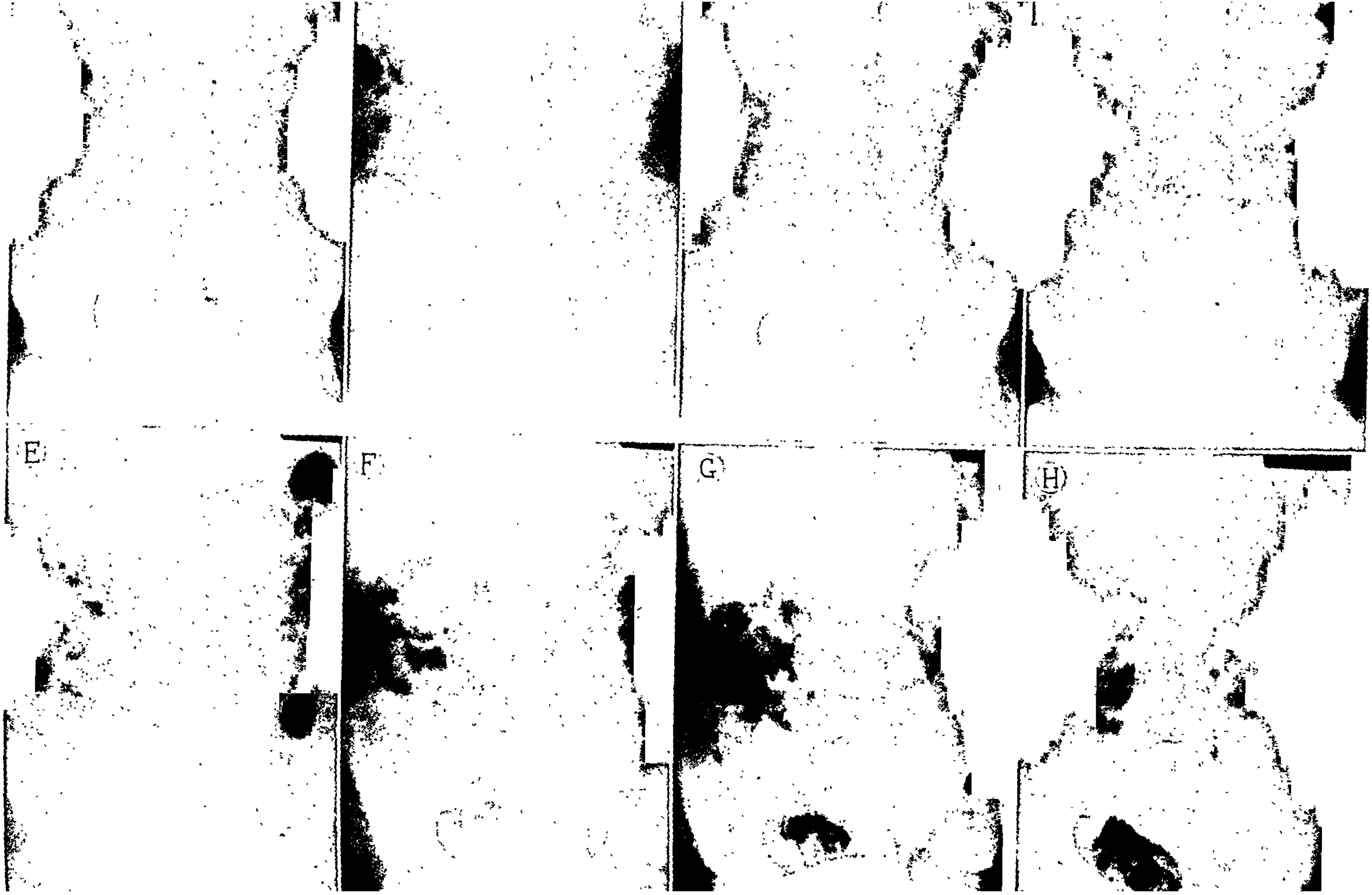
history of recurrent chills, fever and pyuria Residual bladder urine has never been proved in either child and each voids a prompt, full, forceful, uninterrupted stream which is started and maintained without straining Excretory urograms and retrograde pyeloureterograms were interpreted as normal Voiding cystoureterograms revealed bilateral hydronephrosis and hydroureters in the male child and a large unilateral hydroureter and hydronephrosis in the female child

TREATMENT

Transurethral or open surgical removal of bladder neck obstructions should be done promptly to eliminate residual bladder urine and to halt progression of ureteral and renal reflux dilatation Regression of upper tract dilatation following surgical revision of the vesical outlet may be partial or, in occasional instances, complete Often no demonstrable regression of dilatation will occur but if the progress of renal dilatation is halted by surgical correction of the obstructed bladder outlet, then the result may be classified as successful

The regimen is the same for all patients in whom reflux occurs while voiding, whether they do or do not have vesical neck obstruction It is obvious that patients with obstruction are not placed on the following voiding schedule until after the obstructed bladder outlet has been surgically corrected

Children are coached to void at 2 hour intervals during the day and are awakened to void twice during the night They must be constantly admonished to void without straining, "to let the urine run out naturally and without holding the breath and without pushing, straining or hurrying " Fluids by mouth are stopped at 5 p m This regimen has been remarkably effective in the control of pyuria and the decrease in the amount of voiding reflux has been appreciable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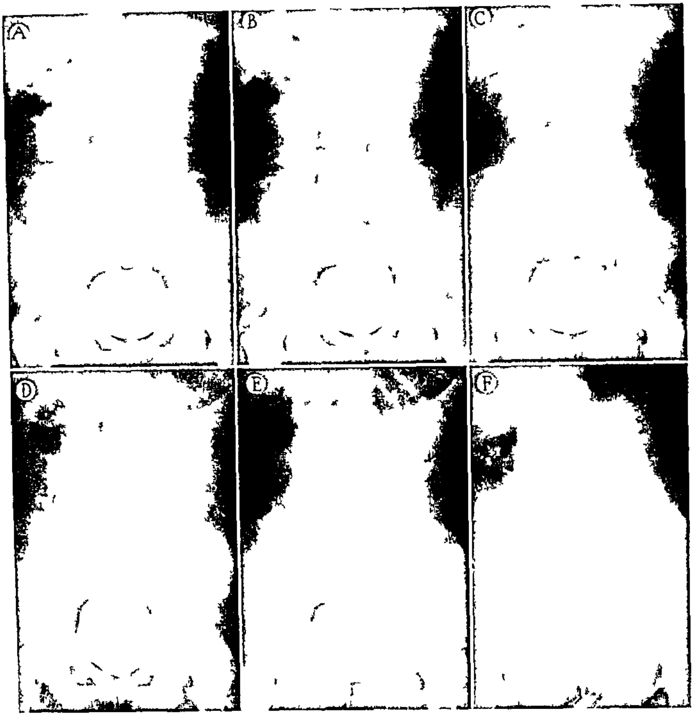

Fig 8 Same case as figures 4, 5 and 6 After 3 months of treatment, as outlined on p 755, these delayed cystographic and voiding cystoureterogram studies were recorded following instillation of 250 cc 20 per cent urokon into bladder

A, *B* *C*, *D*, *E*, delayed cystogram Exposures taken in supine position immediately (*A*) and at 15 minute intervals for 1 hour (*B*, *C*, *D*, *E*)

F voiding cystoureterographic exposure taken with patient in upright position while voiding forcibly Improvement apparent on comparison of pre and post treatment film studies

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F 1, 2 and 3 Comparative delayed cystographic and void ing after 3 months of 2 hour, non straining voiding regimen desc 755)

A, delayed cystographic studies after instillation of 300 cc 20 per cent urokon into bladder through catheter Five minute exposure

B *C* *D* and *E*, exposures taken at 15 minutes and at 15 minute intervals thereafter for 60 minutes Exposures made with patient in supine position Vesicoureteral reflux did not occur at any time during this 1 hour interval as it occurred during preceding delayed cystographic studies (figs 1 and 2)

F and *G* films exposed with patient in upright position while forcibly voiding Bilateral reflux occurred but not so complete as recorded in preceding voiding cystograms (fig 3)

H, after voiding film showing absence of residual urine in bladder

Film studies (figs. 7 and 8) show the voiding reflux findings after 3 months of this regimen.

CONCLUSIONS

The following facts and impressions result from 7 years' experience with delayed cystography and 2½ years' experience with voiding cystoureterography.

The degree to which the bladder is distended with contrast medium during a prolonged period evidently bears no relation to whether or not reflux will 1) occur, 2) be immediate, 3) be delayed, 4) be recurrent, 5) be unilateral, 6) be bilateral, or 7) occur during voiding.

Over-distension of the bladder is not necessary for the demonstration of reflux during delayed cystography or voiding cystoureterography.

Reflux, immediate, delayed, recurrent or voiding, does not occur in a normal urinary tract. It occurs in some cases in which the pathological cause may not be demonstrated, but a pathological process of some undemonstrable or as yet unrecognized type is still believed to be present, and to be the cause of the reflux.

It is impossible to predict reflux competence or incompetence of a ureteral orifice on the basis of its cystoscopic appearance. Reflux may readily occur through orifices having every visual physical attribute of competence when observed cystoscopically. Reflux may not necessarily occur through a gaping golf-hole type of ureteral orifice which has the accepted visual appearance of complete reflux incompetence.

Delayed cystography and voiding cystoureterography have repeatedly proven that intravenous urograms and retrograde pyelograms may be completely misleading. Far advanced ureteral and renal dilatation has been demonstrated by these cystographic techniques in patients having comparative intravenous and retrograde studies which were interpreted as normal.

Urinary infections, continuous or recurrent; neurogenic defects, congenital or acquired; prenatal structural and functional variations from the normal; and postnatal obstructive uropathies may contribute alone or in variable combinations to the cause and occurrence of ureteral reflux. It is probable that the obstructive lesions which undoubtedly initiate and cause the persistence of these reflux phenomena may vary to a degree not previously suspected. It is possible that unrecognized minor congenital displacements and malformations, in combination with neurogenic defects of minor degree, may result in some major variations in vesicoureteral physiology.

Voiding ureteral reflux has been shown to persist in some patients even after the complete surgical removal of the reflux initiating bladder neck obstruction. It is believed that continued or recurrent pyuria, in children whose previously existing vesical neck obstructions have been surgically removed, may be the direct result of the persistence of this voiding reflux phenomenon. In these instances, it has become easier for the bladder to void a portion of its contained urine back up into the upper urinary tract than out through a surgically corrected, unobstructed vesical neck. Infection will persist or recur in these patients until some type of infallible corrective surgery is devised to prevent ureteral reflux.

Reflux does not occur immediately or delayed in some cases in which findings at cystoscopy dictate its occurrence (i e , golf-hole ureteral orifices) This finding is usual in those cases of chronic upper urinary tract dilatation in which the ureter has reached the maximum of dilatation in width and further dilatation can only be manifest by an increase in ureteral length This increase in length occurs within the confines of the periureteral fascia and the resultant kinking of the ureter causes intrinsic ureteral obstruction These ureters cannot be drained by manual pressure when they are surgically exposed until the kinks have been released by lysis of the periureteral fascia Following the removal of the periureteral fascial confines, these ureters drain promptly and peristalsis is readily demonstrated The ureteral diameter will often decrease to one fourth the previous diameter following ureteral fascial lysis It must be concluded that reflux cannot be expected to occur upward in a ureter which is obstructed by kinking within its own fascia if prompt drainage downward can be shown to be impaired for the same reason

Cystography, delayed or voiding, provides certain diagnostic information which is unobtainable by any other method It is hoped that this presentation will encourage more widespread use of this simple x-ray technique It is becoming increasingly obvious that many of our previously accepted concepts of the physiology of the vesicoureteral junction have been based upon wishful flights of fancy rather than established facts

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THE FIRST REPORTED CASES OF HUMAN BLADDER TUMORS DUE TO A NEW CARCINOGEN—XENYLAMINE

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Rehn,[1] in 1895, was the first to describe industrial bladder tumors in workers in the aniline dye industry in Germany. These tumors were especially prevalent among the workers in fuchsin. Apparently his findings were not generally accepted for another 10 years, but then much fruitless research began in an effort to identify the carcinogenic agent. Grandhomme[2] listed the acute symptoms of aniline poisoning and noted the presence of hemoglobin in the urine but was unable to identify any toxic agent. Engelhardt[3] showed that aniline was converted to aniline black in the body and eliminated in the urine as the fixed alkali salt of paramidophenyl ether sulfate, which had no carcinogenic property. Schwerin[4] also was unable to identify any causative agent. Adler[5] and Engel,[6] working independently, were unable to find any toxic substance derived from benzidine.

Later, Schar[7] and Pearlman[8] were able to show that the continuous inhalation of small amounts of 1-naphthylamine or 2-naphthylamine would produce bladder carcinomas in rabbits although they were unable to demonstrate the carcinogenic agent in the urine.

It was suggested much later by Walpole, Williams and Roberts[9] that other substances, notably high boiling aromatic amines, as well as 2-naphthylamine and possibly 4-aminodiphenyl, were the carcinogenic factors responsible for the bladder tumors among the German dyestuff workers which had been attributed to aniline.

It is now known that the following chemicals are capable of producing bladder tumors when fed to dogs: 2-naphthylamine, benzidine, N-acetyl-2-aminofluorene, N:N-dimethyl-4-aminoazobenzene, 4-amino-3:2′-azotoluene and xenylamine. These experiments are summarized in table 1.

More recent experimental work has helped clarify many of the problems concerned with 2-naphthylamine. Wiley has shown that 2-naphthylamine in dogs is excreted as 2-amino-1-hydroxyl naphthalene conjugated with sulfuric acid and has suggested that the metabolic products are carcinogenic. The entire subject has recently been reviewed by Bonser, Clayson, Jull and Pyrah[10] who state

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Read at annual meeting, American Urological Association, Los Angeles, Calif. May 18, 1955.

[1] Rehn, L.: Arch. klin. Chir., **50:** 588, 1895.

[2] Grandhomme: Internat. Lab. Office Rep., p. 22, 1921.

[3] Engelhardt: Quoted by Rehn.[1]

[4] Schwerin: Zentralbl. f. Gewerbehygiene, **8:** 64, 1920.

[5] Adler, O.: Arch. f. Exper. Path. u. Pharmakol., **58:** 167, 1907–1908.

[6] Engel, H.: Zentralbl. f. Gewerbehygiene, **8:** 81, 1920.

[7] Schar, W.: Le cancer, **7:** 205, 1930.

[8] Pearlman, S. and Staehler, W.: Klin. Wchnschr., **11:** 1, 1932.

[9] Walpole, A. L., Williams, M. H. C. and Roberts, D. C.: Brit. J. Indust. Med., **9:** 255, 1952.

[10] Bonser, G. M., Clayson, D. B., Jull, J. W. and Pyrah, L. N.: Brit. J. Urol., **26:** 49–52, 1954.

TABLE 1

Chemical	*Animal*	*Amount*	*Appearance T*	*Investigator*
2 Naphthylamine	Dogs	15 gm	6½ yrs	Gehrmann, Foulger and Fleming, Proc 9th Internat Cong Industr Med, London, 1948, p 472 Bristol Wright
2 Naphthylamine	Dogs	"massive"	3½ to 5 yrs	Bonser, Jr, J Path and Bact, 55: 1, 1943
2 Naphthylamine	Dogs	58–130 gm	1½ yrs	Hueper and Wolfe, Am J Path, **13**: 656, 1937 Hueper, Wiley and Wolfe, J Industr Hyg, **20**: 46, 1938
Benzidine	Dogs	325 gm	7 to 10 yrs	Spits, Magnigan and Dobriner, Cancer, **3**: 789, 1950
2 Acetylamino fluorene	Dogs	90–198 gm	5 to 8 yrs	Morris and Eyestone, J Nat Cancer Inst, **13**: *1139, 1953*
N N dimethyl-4 aminoazobenzene	Dogs		2½ to 4 yrs	Nelson and Woodard, J Nat Cancer Inst, **13**: 1497, 1953
4 Amino 3 2′ azo toluene				
4 Aminodiphenyl	Dogs	30 34 gm	2¾ yrs	Walpole, Williams and Roberts, Brit J Industr Med, **11**: 105, 1954

that tumors do not occur in man from 2-napthylamine itself but from its metabolic product, 2-amino-1-naphthol sulfuric acid They base their views on the facts that the oral ingestion of 2-naphthylamine produces cancer only in the bladder and that bladder cancer will not develop if 2-naphthylamine is introduced submucosally in the bladder, and skin cancer cannot be induced by subcutaneous 2-naphthylamine They further suggest that since the cancer-producing amines produce tumors distant from the site of application of the carcinogen, it is the metabolic products that are the active agents Chemically, these carcinogens have similarity of structures with the position para to the amine group on the ring being blocked by a large substituent group

Bonser, Clayson and Jull[11] have shown experimental reasons, at least, why the bladder is so frequently the site of tumor formation Using one of a small group of carcinogenic aromatic amines, 2-acetyl amino fluorine, it is possible to estimate the 2-amino-1-naphthol conjugates by a method developed by Clayson[12] in 1950 It was possible to correlate the relative susceptibilities of the dog, mouse, rat, and rabbit with the amount of 2 amino-1-napthol conjugates which these species excrete It was also shown that the concentration of these conjugates in the urine as compared to the blood plasma was 200.1 This would seem to definitely rule out an earlier belief that the carcinogens reach the bladder by the bloodstream and are not carried there in the urine Huggins and Smith[13] have suggested that the sulphatases in urine may be responsible for releasing the metabolite in active form. Scott and Boyd[14] have shown that diversion of the urine to a sigmoid loop bladder prevents the development of bladder tumors in dogs fed 2-naphthylamine which is further confirmatory evidence that the carcinogenic agent reaches the bladder in the urine.

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[11] Bonser G Clayson, D B and Jull, J W Lancet, 2 286, 1951
[12] Clayson D B Biochem J, 47: 96, 1950
[13] Huggins, C and Smith, D R J Biol Chem, 170 391, 1947

Jull in 1951[15] introduced a possible experimental method of definitely proving the direct carcinogenic action of any suspected substance on the bladder epithelium. Using paraffin wax pellets with a melting point of 56° C., suspected materials were incorporated and introduced into the bladder of experimental animals, entirely eliminating the intermediary action of the liver in metabolism. Using 20 methyl cholanthrene in situ 25 weeks, tumors were obtained resembling those obtained by oral 2-naphthylamine. (The same results were obtained in 3 mice by 2-amino-1-naphthol HCl. The latter is a hydroxy derivative of an aromatic amine.)

The only known experimental report on 4-aminodiphenyl (xenylamine) appeared in 1952 by Walpole, Williams and Roberts.[16] In 1862, Hofman isolated 4-aminodiphenyl from aniline residues. Jackson also isolated naphthylamine from similar residues. Examinations of present day residues from aniline do not show the presence of either naphthylamines or 4-aminodiphenyl. (Using 3:2′-dimethyl 4-aminodiphenyl and 4-aminodiphenyl injected subcutaneously into rats, 1 rat developed papilloma of the bladder with 3:2′-dimethyl-4-aminodiphenyl.)

DISCUSSION

To our knowledge, xenylamine has been produced regularly in tonnage quantities in only one chemical plant in the United States. Production was begun in 1935 and continued with few interruptions through early 1955. The process involved the chemical reduction of para nitrobiphenyl to the finished product, xenylamine or 4-aminobiphenyl. During most of the twenty years of production, the raw material was received in railway tank cars, and pumped to receiving tanks, to the reactor where reduction was accomplished, through several additional vessels for removal of catalysts and by-products, and then pumped to product receiving tanks or to tank cars for shipment. The pipelines and processing equipment thus comprised a "closed" system essentially, with opportunity for potential exposures limited to several points where control analysis samples were taken, where distillation residues were removed from equipment at intervals, and where leaks occurred in pumps and other equipment before repairs could be made. Major repairs to equipment and infrequent accidental spills of the product, rather than normal daily operating conditions, undoubtedly resulted in exposures of major significance.

The finished product was transferred to a second chemical plant where additional processing was carried out. At this plant, the tanks cars were heated with steam coils to make the product fluid and the xenylamine was pumped to receiving tanks and thence to a reactor or kettle with an open top. At this point, pre-

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[14] Scott, W. W. and Boyd, H. L.: J. Urol., 70: 914, 1953.

[15] Jull, J. W.: Brit. J. Cancer, 5: 328, 1951.

[16] Walpole, A. L., Williams, H. C. and Roberts, D. C.: Brit. J. Industr. Med., 9: 255, 1952.

XENYLAMINE

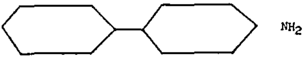

FIG 1

sumably adequate exhaust ventilation was provided Again, except for the earliest period of production, routine exposures were not excessive when compared with industrial exposures to many other organic amine and nitro compounds

In both plants, as technology and science progressed, improvements were made in operational procedures resulting in progressively less exposure to personnel It is doubtful if the magnitude of the exposure that caused the systemic injuries described in this paper will ever be determined It is believed, however, that routine day-to day exposures in recent years were limited to the attainable minimum

As shown in figure 1, xenylamine or 4-aminobiphenyl, is a molecule made up of two joined benzene rings with an NH_2, or amine group, attached to a carbon atom in para position to the junction of the rings with a molecular weight of 169 22 It is a yellowish-brown crystalline solid which melts at approximately 50°C and boils at more than 325°C, and the distillation range is 325°C to 340°C

Following acute exposure, xenylamine produces symptoms experienced with most aromatic nitro and amine compounds Presumably, absorption from the alimentary tract of man would be as dangerous as in the case of animals In rabbits, the oral LD_{50} has been reported as 690 milligrams per kilogram By comparison with many other industrial chemicals, this is not a highly toxic compound from the standpoint of ingestion nor would absorption of the material from the gastrointestinal tract be of practical significance in relation to industrial exposures It is known, however, that in man, xenylamine is rapidly absorbed through the unbroken skin and the vapors from the compound are readily absorbed through the respiratory tract Following acute exposures to the material of the skin or to the vapors, workmen have developed headaches, lethargy, cyanosis, and in the case of heavy exposures, hematuria All of these symptoms may result from excessive exposure to many simple aromatic amino and nitro compounds which are not known to be carcinogenic

CLINICAL FINDINGS

As soon as it was realized that xenylamine might be responsible for the production of several bladder tumors that had developed among the workers, routine cystoscopic examination of all the men who had been exposed in any way to xenylamine was carried out The histories of the workers were highly significant in that some had noted one or more attacks of gross hematuria, usually associated with burning and frequency of urination At the present time, however, it has been impossible for us to correlate the degree of urinary irritative symptoms and hematuria with the later development of bladder tumors

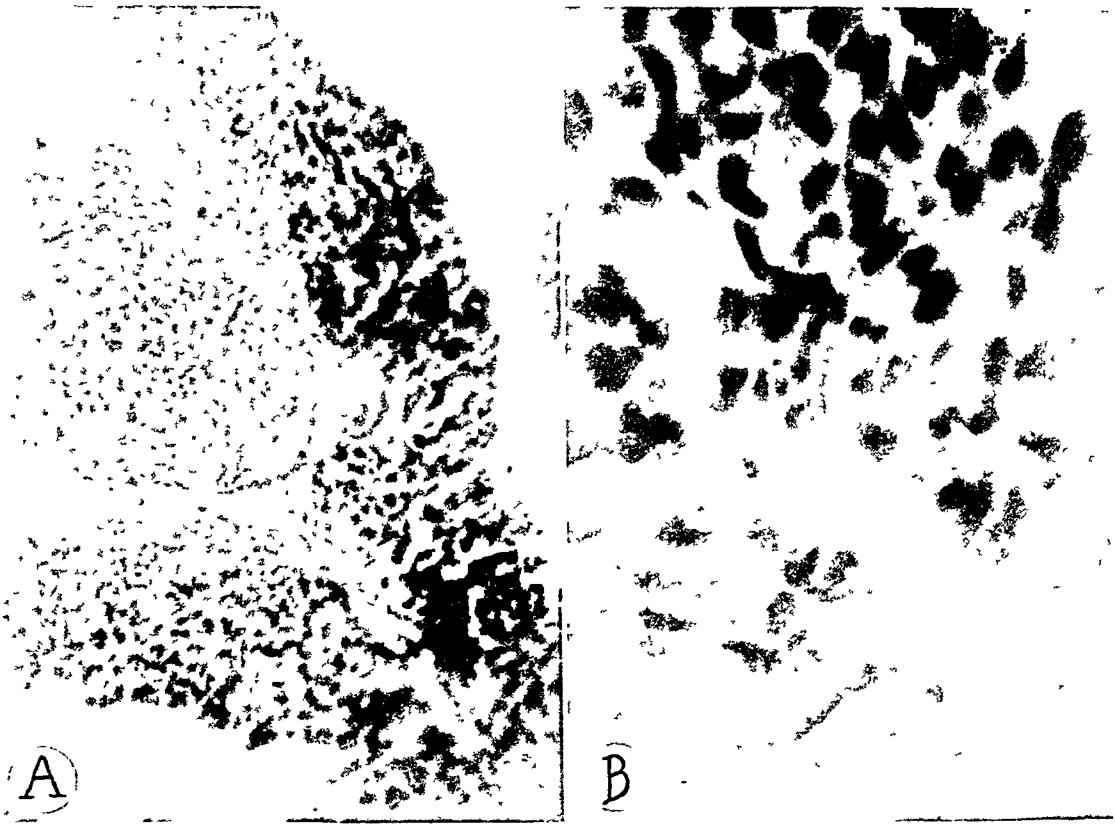

Fig. 2. Photomicrographs. *A*, low power section of bladder tumor removed transurethrally from case No. 254410D. *B*, high power section of bladder, same case as *A*.

Routine observation cystoscopy disclosed that a number of the patients had no detectable signs of bladder irritation. Others had marked evidence of hyperemia, with patchy areas of edema, some of which were raised above the surface of the surrounding mucosa. In order not to miss any early tumors, many of these were biopsied with a cold rongeur and the base fulgurated. The pathological picture was the same, of marked hyperemia, infiltration with inflammatory cells, and marked evidence of hyperkeratosis. A few of the bladder tumors appeared as simple ordinary papillomas, but were apt to be found in any area of the bladder, and not limited particularly to the ureteral or trigonal regions. The majority appeared as flat, sessile lesions surrounded by areas of hemorrhage and hyperemia. In order not to distort the pathological picture, all were removed with a cold cutting rongeur. There was some local evidence of invasion of the muscularis which agrees with the previously reported statements, "in experimental bladder tumors distant metastases are rare but local invasion is common" (Hueper, Briggs and Wolfe; Stirling, and Ash; and Waller and Hamer).[17, 18, 19]

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[17] Hueper, W C., Briggs, J. G. and Wolfe, H D.: J Ind. Hyg. and Toxicol , **20**: 85, 1938
[18] Stirling. C. and Ash, J E : J. Urol , **45**: 342, 1941
[19] Waller, J. I. and Hamer, H. G : J. Urol., **64**: 651, 1950.

TABLE 2

Case Identity		Detected	Exposure Dates	Duration of Exposure
#1254	AB	1953	1938–present	15 yrs.
#1249	AB	1953	1936–1939	3¼ yrs.
#140453	L	1954	1939–1941	2¼ yrs.
#1506	AB	1953	1941–1944	2½ yrs.
#1896	AB	1951	1940–1942	1½ yrs.
#1505	AB	1953	1940–1941	1½ yrs.
#1267	AB	1954	1949–1951	1¼ yrs.
#254410	D	1954	1935–1944	9 yrs.
#245	AB	1954	1935–1950	15 yrs.
#2866	AB	1953	1940–1941	1⅓ yrs.
#1073	AB	1955	1941–1946	1½ yrs.
#813	AB	1954	1946–1948	Intermittent, 8 yrs.

AB—Alexian Brothers' Hospital, St. Louis, Mo.
D—Evangelical Deaconess Hospital, St. Louis, Mo.
L—Lutheran Hospital, St. Louis, Mo.

TABLE 3

Case Identity*	Detected	Exposure Dates	Duration of Exposure
17830	1953	1944–1954	10 yrs. (approx.)
107896	1946	1937–1944	7 yrs.
27641	1946	1939–present	16 yrs.
27442	1954	1949–1954	Intermittent
22093	1952	1936–present	19 yrs.
18129	1952	1943–1945	2 yrs.

* Patient number (HME).

TABLE 4

	Group 1	Group 2
Number patients examined	71	44
Number with normal bladders	18	23
Number with evidence of irritation	42	20
Number with tumors (proven with biopsy)	12	1
Per cent tumors	16.9	2.6

TABLE 5

	Number of Men Examined	Number of Tumors Found	Examiner	Per Cent Tumors
	56	6	HHE	10.7
	71	12	M & N	16.9
	44	1	M & N	2.3
Totals	171	19		11.1

One case found and treated by another urologist.

The microscopic examination of the tumors showed varying degrees of malignancy, but the most marked microscopic finding was the hyperkeratosis, evidently the response to a markedly irritating substance. The presence or absence of tumors before cystoscopic visualization could not be correlated with the presence or absence of red blood cells in the urine. Time does not permit discussion of treatment, but all except two of the patients have been controlled by transurethral measures.

The first opportunity of visualizing the immediate effects of xenylamine came on July 15, 1954. An employee, G. D., helped repair a "breakdown" in the manufacturing equipment the day previously, and it was reported that he had not used the proper precautions that had been outlined by the company. Within eight hours the patient noted an intense urinary burning and frequency followed by marked hematuria. He was immediately placed on antibiotics and observation cystoscopy carried out one day after exposure. The entire interior of the bladder was intensely hyperemic, with many areas of slough and frank hemorrhage. The symptoms slowly disappeared over the next two weeks and the urine became clear. When examined 3 and 6 months after exposure, the entire reaction had disappeared and the bladder mucosa had become entirely normal. He is being followed closely to determine the late effects, if any, after this single massive exposure. A low and a high power photomicrograph of a representative tumor are shown in figure 2. The entire experience with these tumors is outlined to date, together with the potential lengths of exposure in tables 2 to 5.

SUMMARY

Xenylamine, an aromatic amine, produces bladder tumors in experimental animals with relatively brief exposures.

Bladder tumors have already developed in 11.1 per cent of 171 workers engaged in the production of xenylamine from 5 to 19 years after their initial exposure.

The duration of exposure to the compound varied in these 19 workers from 1¼ to 19 years.

The exact carcinogen has not, as yet, been identified, but it is reasonable to assume that it is some metabolite of 4-aminobiphenyl. Experimental work is under way regarding this point and will be reported at a later date.

Xenylamine apparently gains access to the body through the skin or respiratory system, and the immediate effect on the bladder is a diffuse hyperemia, edema, and frank slough. This is followed by an unknown interval during which the bladder mucosa may return to complete normal appearance.

Careful, systematic survey of all of the workers has been set up and the results of this will be reported at a later date.

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THE USE OF RADIOACTIVE COBALT IN NYLON SUTURES IN THE TREATMENT OF BLADDER TUMORS TECHNIQUE AND CASE REPORTS

VINCENT VERMOOTEN AND J G S MAXFIELD

The management of carcinoma of the bladder has always been a serious problem, that it is still unsolved is evident from the recent literature The February 1955 issue of the *Journal of Urology* contained 6 articles on tumors of the bladder, five of these were in regard to treatment Two additional articles in the March issue concerned treatment of bladder tumors Although all these papers dealt with treatment, the method and agent used were different in each report, yet none referred to cystectomy in any form This suggests that there may be a definite swing away from the more radical approach to our problem

Recently we have been using a new method of applying radiation with which we have had excellent results and which we now believe is the ideal technique *for radiation of infiltrating bladder tumors This particular method of radiation* is not recommended for general use for all types of bladder tumors as there are many which can be treated more efficiently and satisfactorily by other means There is, for instance, no point in using this type of radiation therapy in patients with multiple papillomas, for we feel that this is a disease of the entire urothelium and, therefore, treatment of a single lesion will not cure the disease

External radiation of bladder tumors before the recent advent of supervoltage machines and of the radioactive kilo Curie cobalt units has not been particularly satisfactory, but the local application of radium or source radium emanation has been successful for a long time In 1911 Paschkis described his cystoscopic radium applicator for use in treating cancer of the bladder There has been no subsequent report on the use of his instrument In 1913 Pasteau and Degrais and also Schuller reported a few cases of cancer of the prostate and bladder in which truly striking results had been obtained by the use of radium introduced through the urethra through the ordinary gum coudé catheter The next year Hugh Young (not knowing the existence of Paschkis' instrument) invented his cystoscopic radium applicator and began treating bladder tumors with 100 mg capsules of radium The treatment lasted for an hour at a time and the patients were given from 600 to 1000 milligram hours of radiation depending on the type of tumor In 1917 Young successfully treated a bladder tumor in a woman by implanting into the tumor, through his endoscope, 200 mg of radium in a rigid needle In 1922 Neill devised an instrument for implanting seeds of radium emanations directly into the tumor through an endoscope This method of radiation has the advantage that when once implanted the seeds need not be removed Failure to get adequate radiation for purely technical, if for no other reasons led to either the radium element or emanations being embedded in the tumor at the time of open surgery This gave and still gives excellent results but here too there are difficulties One can guess but one cannot be sure as to the exact loca-

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Read at annual meeting American Urological Association, Los Angeles, Calif May 19, 1955

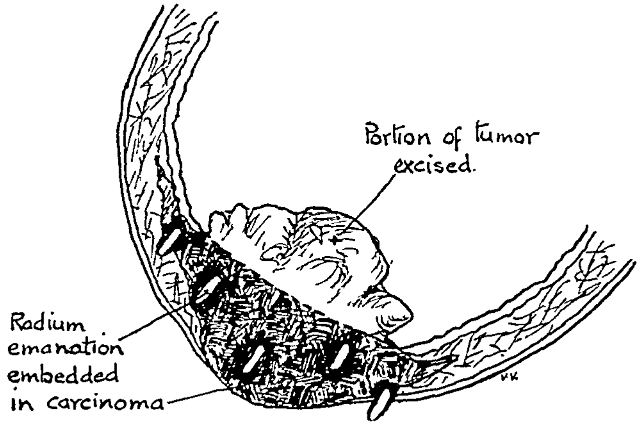
Portion of tumor excised.
Radium emanation embedded in carcinoma
VK

FIG. 1. Depicting probable position of radiation emanations or radium needles embedded in carcinoma of bladder after removal of protruding portion of growth.

tion of the radium or emanation seeds in relation to the tumor (fig. 1). Also, it is well nigh impossible to get a uniform radiation pattern in placing the seeds or needles. The distance of each needle or seed from the next will depend on whether the bladder wall was on a stretch or not when the radiation source was implanted, and subsequently on whether the bladder contains urine and how much or whether it is empty and collapsed. This will also vary with the extent of infiltration of the bladder wall by tumor. The bladder wall may be fixed and inelastic when greatly infiltrated with tumor or it may be flexible when only islands or strands of tumor cells are present. The use of curved radioactive cobalt needles, as described by Binnie and Bates, is far more satisfactory.

Radioactive cobalt in nylon tube sutures answers most, if not all of these problems. The nylon tube suture containing the radioactive cobalt is soft and flexible; one can tell exactly where it is placed; it will follow the contour or shape of the bladder. Each suture can be placed approximately parallel to and one centimeter from the next. As many sutures as are necessary may be used. A uniform radiation pattern can be obtained. One additional great advantage is that tumor can be removed from the bladder surface to thin the bladder wall down to less than one centimeter in thickness and the suture placed as a planar implant. The result is that the entire tumor mass is adequately irradiated and best of all the radiation is effective to the outside of the bladder wall. All cells infiltrating the bladder wall thus receive relatively uniform as well as adequate radiation to produce a carcinocidal effect.

To date we have treated 10 cases by this method. Three have died; one, J. E. (Maxfield Hospital No. 3450), a 60-year-old severe cardiac, died 48 hours after surgery from acute myocardial failure. He had had two previous attempts at segmental resection of the bladder with subsequent recurrence. Another, C. C. (see p. 771), had a severe chill while fishing 6 weeks after his operation and died within forty-eight hours. A third, C. Z. (previously reported) died in uremia 15 months after cobalt implantation. Recurrent extravesical carcinoma eventually obstructed the distal portion of both ureters. All the others are well and are clinically and cystoscopically free from tumor.

Six of these cases were reported in detail at the meeting of the South Central

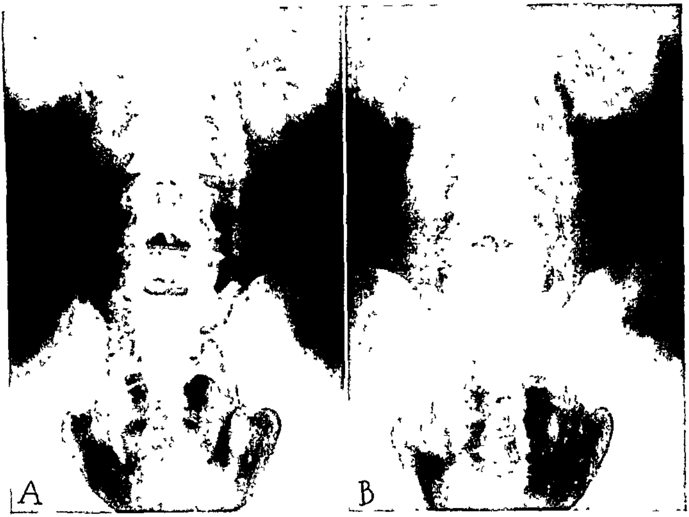

FIG. 2. A, 20-minute preoperative excretory urogram made November 1952. Note ureterectasis and small bladder due to extensive infiltrating carcinoma. *B*, 7-minute postoperative *urogram made April 1955 (2½ years after treatment with radioactive cobalt in nylon sutures)*. Note normal left kidney and ureter.

Section of the American Urological Association in October 1954. A detailed report of our first patient, J. F., has been published. He was a 48-year-old man with an extensive infiltrating carcinoma of the bladder. Figure 2, *A* shows the appearance of the urogram made when he was first seen. Note the contracted bladder of very small capacity (75 cc) and the dilated, partially obstructed left ureter. Figure 2, *B* shows an excretory urogram made April 4, 1955, about two and one half years later. Note the normal left kidney pelvis, calyces and the normal ureter. Cystoscopically there is a small area of radiation necrosis near the air bubble but no evidence of tumor. His bladder capacity is 275 cc. Papanicolaou stain of the urine fails to reveal any malignant cells so we may assume that at this time the patient, who 2½ years ago had an extensive infiltrating urothelial cell carcinoma of the bladder, grade 3, and a recurrence 6 months later which required a second implantation of Co^{60}, is clinically free from carcinoma 2 years after this second implantation of radioactive cobalt. Symptomatically he is well and leads a normal life.

Our limited experience has taught us a great deal in regard to the technique of using the nylon tube sutures containing radioactive cobalt. We feel that reporting our experience may help those who would like to use this method of radiation, to avoid some of the difficulties that we have encountered.

THE CHOICE OF PATIENT

Patients with multiple papillomas of the bladder will not be benefited by this type of radiation. On the other hand, the use of tele cobalt therapy, or the

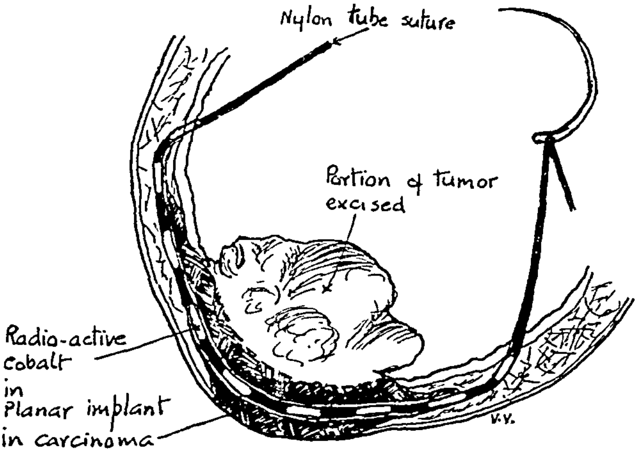

FIG. 3. Depicting planar implant of radioactive cobalt in nylon tube suture after shaving off tumor to leave bladder wall of only 1 cm. thickness.

supervoltage machine may be preferable and more effective, provided the possibility of an associated radiation proctitis is not too great a deterrent. In extensive lesions of this type, Vermooten prefers opening the bladder suprapubically, removing all visible growth with a diathermy loop, fulgurating the base and then instilling 50 per cent phenol in glycerine in the bladder for 60 seconds, as recommended by Kirwin. Small, localized, infiltrating vesical carcinomas that can be easily removed by segmental resection of the bladder (removing twice as much bladder wall as may be indicated), may be removed in that way. However, if there is any doubt that even with a large cuff of normal bladder the entire lesion cannot be removed easily, radioactive cobalt in nylon tube sutures should be used rather than to do an inadequate segmental resection. Any other infiltrating carcinoma for which we would normally do a total cystectomy can be treated by the same technique.

THE COBALT PATTERN

In order to obtain a perfect radiation pattern, the sutures should be parallel to one another and one centimeter apart. The first suture is placed just beyond the very outside edge of visible or palpable tumor. Then each suture is placed parallel to this until one reaches the opposite edge of the tumor. It is always preferable to have some radioactive material in normal bladder tissue rather than to miss a few tumor cells. As long as we are so particular about the accurate placement of the radioactive material in parallel rows one centimeter apart, we feel the depth penetration from front to back should not be neglected. Consequently, the area of bladder that contains carcinoma is freed on the outside so that the surgeon can put his thumb inside the bladder and feel with his fingers from the outside the thickness and extent of the growth or vice versa. When one finds that the carcinoma is more than a centimeter in thickness, it seems wise to us to use the high frequency cutting loop and shave the carcinoma off from the inside of the bladder until the thickness of the bladder wall and carcinoma is less than one centimeter. The needle with the nylon suture attached can then be passed lengthwise into the wall of the bladder through the entire carcinoma, keeping the needle and the suture as close to the outside of the bladder wall as

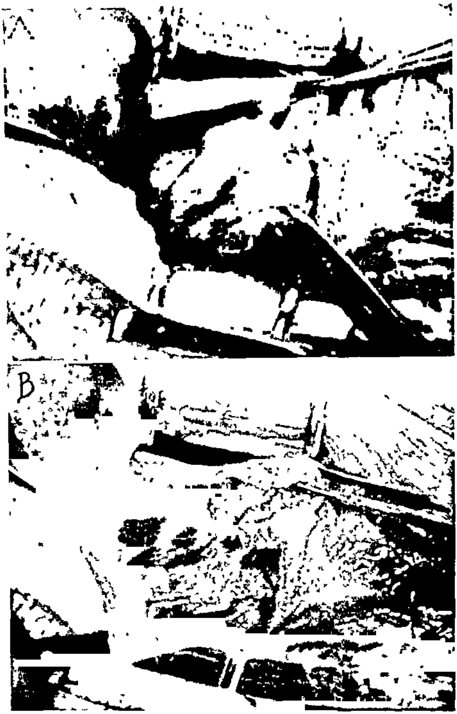

FIG. 4 *A*, extensive infiltrating recurrent carcinoma of bladder. *B*, same patient after shaving off carcinoma and leaving less than 1 cm. of bladder wall thickness.

possible (fig. 3). In this way the actively growing invading cells will receive the greatest intensity of radiation.

This is well illustrated in the following 2 case reports: C. C. (Maxfield Hospital No. 3456) was a 57-year-old man who was admitted to the Hospital November 28, 1954, with a recurrent carcinoma of the bladder. The patient told us that his doctor had removed three-fourths of his bladder 6 months previously. Cystographic and cystoscopic examinations revealed a bladder of only 100 cc capacity with an extensive infiltrating carcinoma involving almost a third of the bladder. On opening the bladder suprapubically a massive, solid, infiltrating carcinoma could be seen (fig. 4, *A*). This was shaved off with a high frequency loop until less than one centimeter of bladder wall thickness was left (fig. 4, *B*). Radioactive cobalt sutures were then sewn into the carcinoma. A very satisfactory cobalt pattern was obtained (fig. 5). The patient made an excellent recovery and 6 weeks later, while fishing, was caught in the rain, had a chill and fever and died 48 hours later.

M. L. (Maxfield Hospital No. 3544) was a 62-year-old woman who was ad-

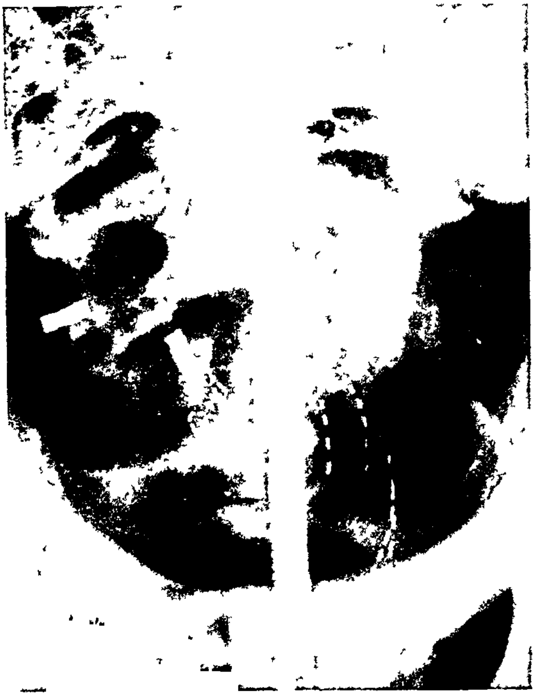

FIG. 5. Postoperative radioactive cobalt pattern in patient, gross photograph of whose tumor is depicted in figure 3.

mitted to Baylor Hospital for diagnosis. She stated that she had been treated with dilatations and silver nitrate instillations for an elusive (Hunner) ulcer for the past ten or twelve years. Cystoscopic examination revealed a bladder of 50 cc capacity and the entire right half of the bladder gave the appearance of thick folds of mucosa. There was no ulceration, no bleeding and the Papanicolaou stain of the urinary sediment was negative for malignant cells. Transurethral resection of some of these folds of tissue for biopsy showed that this was an infiltrating squamous cell carcinoma which had developed from leukoplakia of the bladder. On January 22, 1955, she was transferred to the Maxfield Hospital for radioactive cobalt suture therapy. The bladder was opened suprapubically. More than half of the bladder was involved in the carcinoma. The tumor was shaved off with a diathermy loop until the bladder wall, infiltrated with carcinoma, was only about 0.6 cm. in thickness. Radioactive cobalt sutures were sewn into the carcinoma (fig. 6). The bladder was closed around a 30 cc balloon catheter. When the balloon was inflated it was found that the capacity of the bladder was less than 30 cc. Except for recurring bladder spasms the patient made an uneventful recovery. When examined 3 months later her bladder capacity was 45 cc. No tumor could be seen cystoscopically but the area where the carcinoma had been was still superficially ulcerated.

TECHNIQUE OF IMPLANTATION

In addition to the improvement of radiation uniformity in the patient, the operating team is protected from irradiation during almost the entire course of procedure, since the technique of implantation is as follows: The lead-shielded

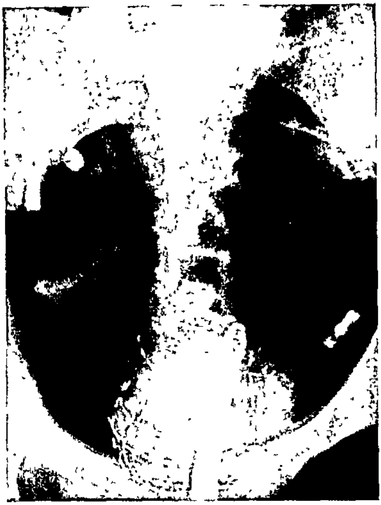

FIG. 6. Preoperative cystogram superimposed on postoperative radioactive cobalt pattern shows how accurately nylon tube sutures containing radioactive cobalt have been placed.

container holding the radioactive material is placed on a Mayo table and brought as close to the operative site as is possible. The long nylon leaders are sutured into their proper relationships and only when the desired pattern has been obtained are the leaders pulled through. Not until all sutures have been properly placed does that portion of the suture containing the radioactive cobalt leave the lead safe to be pulled into position into the bladder wall. After the radioactive cobalt sutures are implanted, the bladder and abdominal wall are closed and the nylon sutures are brought out through the skin on either side of the incision, each a millimeter or two from the next. This is done so that if any change in the radiation pattern is necessary we can tell which suture to shift or to remove. This is occasionally indicated when we find that the radiograph of the implantation pattern shows a localized intensity greater than is desired. This method of being able to remove selective sutures and so prevent "hot spots" has a great advantage over the use of radium emanations or radium needles.

When the desired dosage of radiation has been delivered, the nylon tube sutures containing the radioactive cobalt are removed like ordinary silk worm gut stay sutures. For this purpose, we usually give most of our patients a little sodium pentothal.

In order to prevent generalized radiation cystitis, we insert an indwelling urethral catheter with a 30 cc balloon. This keeps the remainder of the bladder mucosa sufficiently far away from the source of radiation so that the bladder wall remains soft, flexible and normal. It is possible, by inflating or deflating the balloon, to vary the distance between the sutures of radioactive cobalt in in-

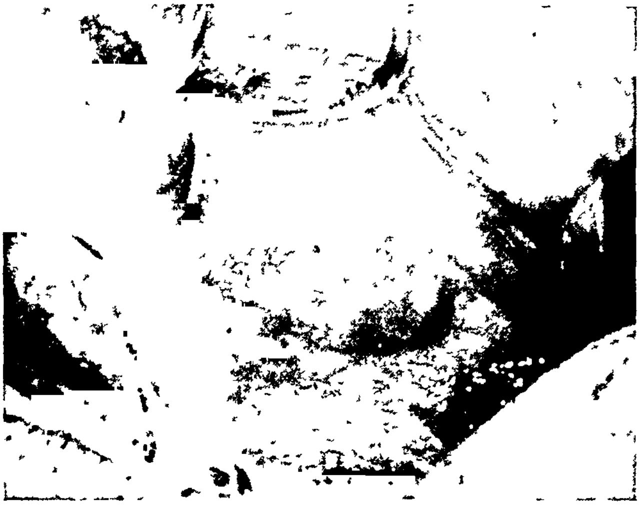

FIG. 7. Photograph at time of surgery shows large, flat surface growing infiltrating urothelial cell carcinoma.

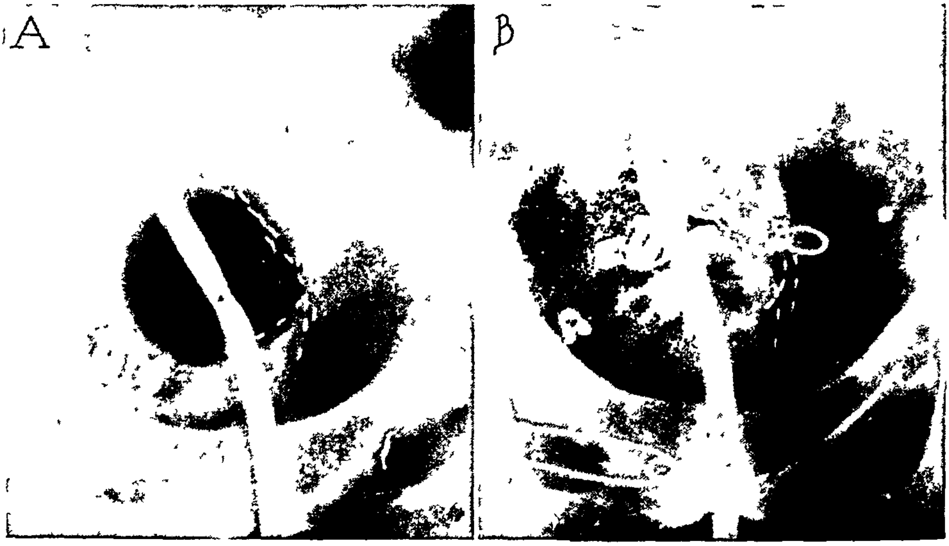

FIG. 8. *A*, postoperative radiograph showing cobalt pattern in same case as figure 7. Note relation of radioactive cobalt to inflated 30 cc balloon *B*, radiograph taken few minutes after that depicted in *A* Balloon has been deflated

stances in which the wall of the bladder is not extensively involved in carcinoma and is consequently still flexible. However, when the carcinoma has caused the bladder wall to be fixed and inelastic, inflating and deflating the balloon merely pushes the normal portion of the bladder away from the source of radiation or allows it to come closer.

Our patient, A. St. A. (Maxfield Hospital No. 3372) illustrates this point. A 62-year-old man was admitted October 4, 1954 for radioactive cobalt suture therapy after cystoscopic examination had revealed a large, flat, surface growing carcinoma (fig. 7) about 6 cm. long and from 2 to 3 cm. in width with only moderate infiltration of the wall of the bladder as indicated by a bladder capacity of 225 cc. After obtaining a biopsy at the time of operation, radioactive cobalt sutures were easily sewn in. With the 30 cc balloon distended with air one sees how accurately the nylon sutures were placed (fig 8, *A*), but with the balloon deflated the pattern changes (fig 8, *B*) The change in the pattern is not quite so marked as it may have been had the carcinoma not infiltrated the wall of the bladder At present this patient is still symptomatically, clinically and cystoscopically well The Papanicolaou stain of the urine is negative for malignant cells

In 2 patients who had severe bladder spasms, we deflated the balloon early with the result that a mild degree of radiation cystitis was present for from 6 weeks to 3 months

THE RADIOACTIVE MATERIAL AND DOSAGE CALCULATION

The radioactive material is cobalt wire cut to form cylinders measuring 3 0 mm in length and 0 5 mm in diameter Each piece of Co^{60} has the amount of radioactivity necessary to produce 2 5r per hour at 1 cm distance (1mc Co^{60} equals 13 5 rhcm) These cylinders are put into a nylon tube and separated from one another by aluminum spacers of the same size Any desired number can be put into a nylon tube so that we have sutures containing 4, 6, 8, 10, 12 and 15 slugs of radioactive cobalt The amount used depends on the length of the area to be treated

Radioactive cobalt has the advantage of having a half life of 5½ years and so it can be used over and over again With radioactive cobalt the gamma radiation is homogeneous (1 16 and 1 31 mev) The small amount of beta radiation is very soft (0 31 mev) Ninety-three per cent of this is filtered out by the nylon This means that there is almost no ionization of the tissue and consequently a soft, flexible scar results In our first patient, as in several subsequent patients, it was necessary to sew the radioactive material right through, as well as alongside, a ureteral orifice yet, as can be seen in figure 2, *B*, the ureteral orifice has returned to normal

The pattern is planned for the radioactive material to be left in place for 7 days The time has varied from 144 hours to 216 hours, depending on the final achieved pattern to produce an estimated dosage of 7000 gamma roentgens to the tumor Radiographs made in stereoscopic, anteroposterior and lateral positions are made 48 to 72 hours after the operation From the final position of the radioactive cobalt as shown by these radiographs, proper calculations using appropriate Paterson-Parker tables are used to determine the time necessary to deliver the desired dosage of 7000 gamma roentgens

The following is a typical calculation

1 *Tumor dose*

A) Implant of 4 cm by 4 cm in bladder wall with 5 sutures used
B) The opposite bladder wall is kept at 4 cm distance from the implant by the use of an inflated 30 cc balloon catheter
C) Nylon tube sutures loaded with 8 Co^{60} cylinders of radioactivity 2 5 rhcm per cylinder This is a total of 20 rhcm per suture No elongation factor to consider
D) Paterson Parker planar implant tables for Co^{60} need 2700 rhcm hr per

1000r for 16 cm^2 area. Number of sutures used—5. Activity per suture—20 rhcm. Total activity $20 \times 5 = 100$ rhcm.

E) From (D) we have 2.7 rhcm hr/roentgen.

F) $\frac{(D)}{(E)} = \frac{100 \text{ rhcm}}{2.7 \text{ rhcm/r}} = 37$ roentgens/hr.

G) Dose rate at plane 0.5 cm. from implant plane assuming P-P distribution is 37r/hr.

H) Time necessary to give 7000r is $\frac{7000r}{37r/hr} = 189$ hrs—(approximately 8 days).

2. *Dose to opposite bladder wall.*

A) P-P surface mold tables at 4 cm. distance for area 16 $cm.^2$ of mold area is 23.5 rhcm hr per roentgen.

B) Total activity from 1. (D) 100 rhcm.

C) $\frac{100 \text{ rhcm}}{23.5 \text{ rhcm hr per r}} = 4.2$r/hr.

D) Total radiation 189 hours × 4.2/rhr = 783.8r

SUMMARY

The technique is described of using nylon tube sutures containing radioactive cobalt in the treatment of infiltrating carcinoma of the bladder.

Four new cases are briefly reported and followup notes are given on 10 cases treated by this method.

Several cases reported illustrate the important details of the technique used.

The method of handling the sutures so that the operating team is not exposed to unnecessary radiation is mentioned.

The advantages of this type of radiation therapy over other types in use at present are demonstrated.

We wish to acknowledge the untiring efforts of D. L. Tabern, Ph.D. and the Abbott Laboratories for supplying us with, and for their help in improving the quality of, the radioactive cobalt in nylon. We also want to acknowledge the valuable help, technical aid, and counsel of George W. Callendine, Jr., Ph.D. and William G. Myers, Ph.D., M.D. of the Ohio State University Medical Center.

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ANGIOMA OF THE BLADDER

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Angioma is the rarest of all bladder neoplasms Less than 50 case reports have appeared in the medical literature since Langhans reported the first one in 1876 Several reviews of the literature, including Macalpine[1] and Segal and Fink[2] had brought the total to over 40 by 1942 We have been able to find cases reported since then by Hyams and Silberblatt,[3] Cawker,[4] de la Peña[5] and Riches [6] The case reported below brings the number to 46 published instances to date

CASE REPORT

A 52-year-old white male taxi driver entered Wesley Memorial Hospital in March 1954 complaining of suprapubic pain which started one month before admission The pain was "gnawing" in character, worse when the bladder was distended, and was relieved by urination He denied hematuria, frequency, pyuria, slowing of the stream or incontinence There had been a loss in libido and potency for 6 years He admitted having had gonorrhea 30 years ago His father and brother had died of cancer

Physical examination was entirely normal except for moderate obesity There was no suprapubic tenderness or mass felt The genitalia and rectal examinations were normal

Laboratory tests included a normal Kahn, blood counts of 4 01 million erythrocytes, 7,250 leukocytes, 13 1 gm hemoglobin and a normal differential Urinalysis showed 2 to 5 leukocytes, an occasional granular cast, and many calcium oxalate crystals The urine culture was negative

A cystoscopy was carried out under sodium pentothal anesthesia, using a 24F Brown-Buerger instrument On the dome of the bladder, just to the left of the air bubble, was seen a small, bluish-brown area which was slightly raised and measured about 5 mm in diameter The surrounding mucosa was hyperemic External suprapubic pressure brought the lesion well down into view for biopsy (fig 1) The remaining tumor and surrounding mucosa were then coagulated The bladder and prostatic urethra were otherwise entirely normal A Foley catheter was left indwelling for 24 hours

The patient was discharged from the hospital on the third postoperative day He remarked about the freedom from pain when the bladder was full The bladder was examined cystoscopically 4 and 8 months later, and there was no

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Accepted for publication June 14, 1955

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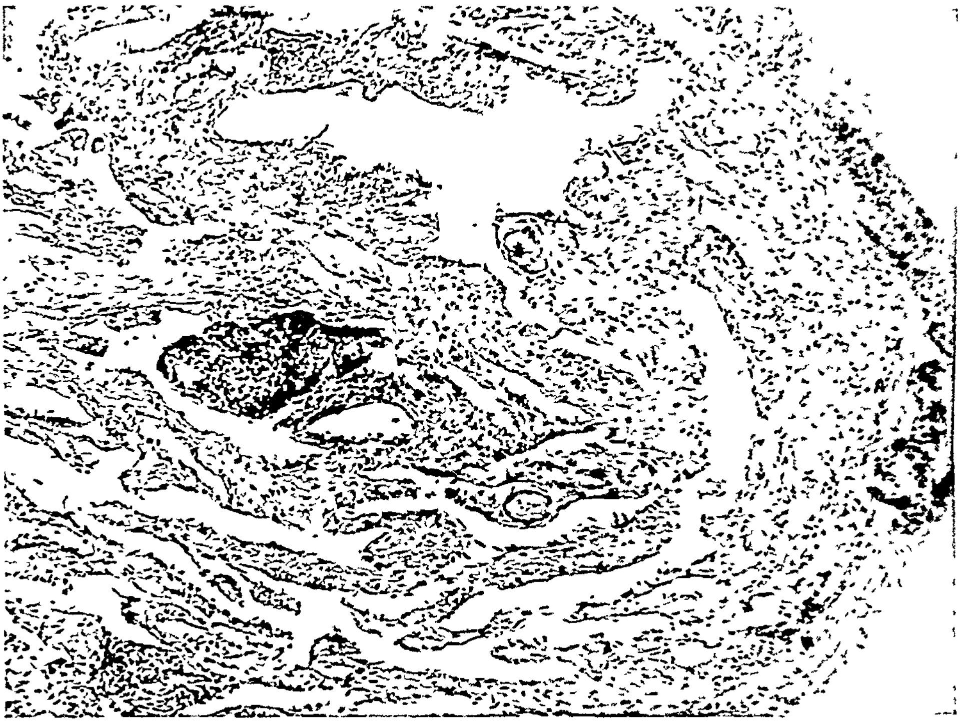

FIG. 1. Biopsy of angioma of bladder

evidence of recurrence at these times. There has been no other angioma found on his body.

Pathology report (Dr. Thomas C. Laipply): The biopsy specimen consisted of several pieces of soft tan tissue averaging 0.1 cm. in diameter. Microscopic sections revealed tissue lined partially by transitional cell epithelium. In the underlying fibrous connective tissue, slight infiltration by chronic inflammatory cells was seen. Also noted were empty spaces which appeared to be lined by a single layer of cells. Additional sections revealed that these spaces were lined by flattened epithelial cells and were supported by a pale eosinophilic fibrous connective tissue stroma (fig. 1). Diagnosis: Angioma.

DISCUSSION

The commonest presenting symptom in bladder angioma is hematuria. The tumors as seen cystoscopically are often bluish-black, irregularly-shaped, sessile and soft. Their size varies from tiny growths localized in the bladder to large masses which penetrate the perivesical tissues. The dome of the bladder is the common site. Lesions on the bladder floor must be differentiated from varicosities. Angiomas elsewhere, both visceral and cutaneous, are not uncommon in these patients.

The smallest tumors can be coagulated transurethrally with safety, but this may be dangerous when the growth is large. The main bulk of the tumor may be well outside the bladder mucosa with only one surface visible cystoscopically. Suprapubic segmental resection or cystectomy is indicated for these larger angiomas, according to the limited experience surgeons have had with the lesion All the angiomas which have been reported have been benign with the exception of the angiosarcoma of Jugano[7]

SUMMARY

A patient with angioma of the bladder is presented and discussed The literature on this rare tumor is briefly reviewed

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THE MANAGEMENT OF SOME LATE COMPLICATIONS OF PELVIC IRRADIATION

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The value of irradiation therapy in the management of pelvic neoplasms has been well established. Improvements in methods of shielding and calculation of tissue dosage have resulted in admirable therapeutic success with minimal complications. A certain number of cases of injury to adjacent organs continue to occur, however, and among these are some which fall to the lot of the urologist to manage. Of these, vesicovaginal fistulas and ureteral obstruction are among the most numerous and most difficult.

VESICOVAGINAL FISTULA

Vesicovaginal fistula, often compounded by involvement of the colon or rectum, with a resultant incontinent cloaca-type of existence for the unfortunate patient, is seen as a late complication of irradiation therapy in 2 per cent of cases of carcinoma of the cervix so treated. The incidence is much higher in diabetic patients, 60 per cent of whom may be expected to have this complication.[1] Associated sepsis, cachexia, and anemia due to infection and continued loss of protein and blood make the problem of reparative surgery seem almost impossible. Attempts to close the large defects in the bladder and vagina often fail because of the extensive fibrosis and atrophy of the tissues secondary to irradiation. In many cases, it becomes apparent that permanent correction of these defects is impossible, and diversion of the urinary and fecal streams becomes necessary. After correction of the depleted protein stores and blood volume by proper diet and multiple transfusions, and control of sepsis by antibiotics and such emergency diversionary methods as nephrostomy, there remains the problem of a permanent type of diversion of the urinary flow.

Nephrostomy itself might suffice, but for its known propensity to renal infection, calculus formation and accidental loss of function, to say nothing of the difficulties of management by patient and physician. This is especially true when bilateral nephrostomy is necessary.

Ureterostomy in situ has not proven itself of much greater value than nephrostomy, for similar reasons.[2]

Cutaneous ureterostomy, with its known difficulties of management and complications of stricture, infection and calculus formation may well be considered a last resort.

Ureterosigmoidostomy, at first thought to be a bright hope for "bladder substitution," has proven to be fraught with the dangers of recurrent pyelone-

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Read at annual meeting, American Urological Association, Los Angeles, Calif., May 19, 1955.

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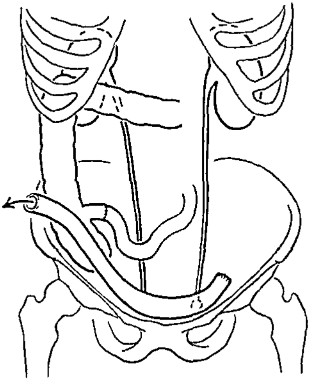

FIG 1 Diagram Ureteroileostomy to isolated segment

phritis[3] The high incidence of recurrent sepsis, anemia, acidosis, and concomitant anorexia has led to the gradual abandonment of this type of urinary diversion by all but the most fortunate or hardheaded of its protagonists The reasons for its failure have become apparent in the past few years Anastomosis of the upper urinary tract to a constantly contaminated viscus, with resultant stricture formation, back pressure, and absorption of urinary constituents, lead to the sequellae mentioned above Almost the same objections are valid for such procedures as the "cecal pouch" type of diversion, and it appears that any method which seeks to provide a reservoir for urine is liable to the complications of infection, renal damage and absorption

The problem then becomes one of providing a satisfactory conduit for urine which will be adaptable to a wide variety of cases, protect the upper urinary tract, and the electrolyte balance of the patient, and provide an acceptable and easily managed stoma

The isolated ileal segment which Bricker[4] has described and found so satisfactory in the management of patients on whom he performed pelvic exenteration, appears to offer such a solution

This method of urinary diversion has been used in 6 cases of vesicovaginal fistula in the past 2 years The results to date are so satisfactory that they are presented as a note of encouragement in an otherwise dark and depressing urologic dilemma

TECHNIQUE

The operative technique is essentially that described by Bricker,[5] with minor modifications (fig 1) A segment of ileum from 12 to 14 inches long is isolated,

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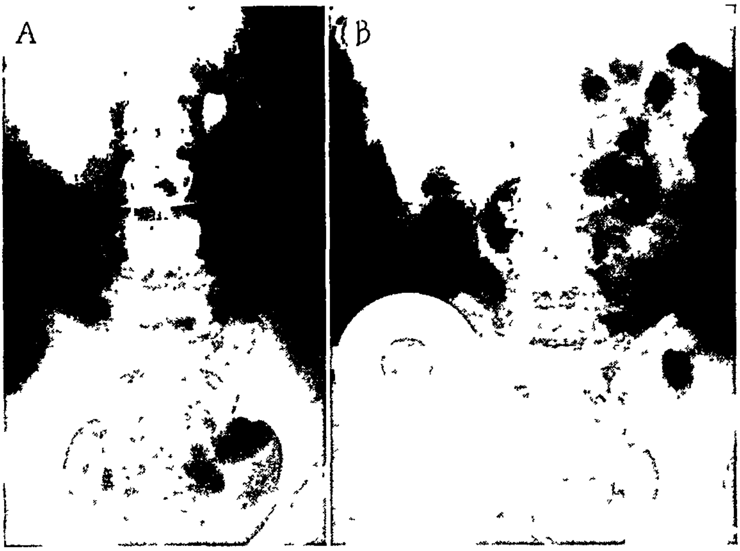

FIG. 2. Case 1. Right hydronephrosis. *A*, *preoperative film*. *B*, *postoperative urogram*. Normal appearing upper tract.

the rule being to bring the bowel to the ureters so that there is no tension on the anastomosis. The proximal end of the isolated segment is closed with two layers of catgut and one of silk. Anastomosis of the ureters to the side of the bowel is performed by the elliptical technique of Nesbit.[6] The anastomosis is supported on the right side by a few sutures of the posterior parietal peritoneum to the serosa of the ileum near the anastomosis, and on the left by tacking the ileal serosa to the sigmoid mesentery to prevent tension on the anastomotic site. The distal end of the ileum is brought through an excised ellipse of skin, fascia and muscle in the right lower quadrant, and the mucosa is sutured to the skin edge. The distal cut edge of the mesentery of the isolated segment is tacked to the lateral parietal peritoneum to prevent internal hernia and retraction of the end ileostomy. No tubes are used in the ileum. A near catastrophe in one of the early cases revealed the danger of plugging by mucus, and at present a Rutzen-type bag or rubber dam is applied immediately. If a rubber dam is used the dressings may be weighed to calculate the urinary output in the postoperative period.

The first case was V.T., University Hospital No. 00-21-67, a 58-year-old woman who had a history of irradiation therapy for carcinoma of the cervix 10 years prior to her first visit to our clinic. At this time she was febrile, anemic, and wasted, with constant urine and fecal drainage from the vagina. Despite repeated biopsies of a large infected, indurated pelvic mass no evidence of recurrence could be found. An intravenous urogram (fig. 2, *A*) revealed right hydronephrosis and a normal appearing left urinary tract. A right nephrostomy resulted in subsidence of the sepsis and her general condition improved on a high protein diet and several transfusions of whole blood. Laparotomy on September 19, 1953 revealed no evidence of carcinoma in the abdomen although there was a good deal of induration in the pelvis. A Devine-type of sigmoid

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[6] Nesbit, R. M : Elliptical anastomosis in urologic surgery. Ann. Surg., **130:** 796–803, 1949.

colostomy was performed. The ureters were anastomosed to an isolated segment of ileum measuring approximately 11 inches in length. The postoperative course was smooth, the drainage from the vagina decreased and she gained weight and maintained her hemoglobin level. Excretory urography prior to discharge on October 7 revealed improvement in the right kidney and minimal evidence of ureteral dilatation bilaterally. She has been followed for 18 months since operation and has shown no evidence of electrolyte disturbance. The most recent urogram revealed bilaterally normal appearing upper urinary tracts (fig. 2, *B*). Repeated determinations of the residual urine in the isolated segment have found between 1½ and 2 ounces.

Case 2, N.S., University Hospital No. 00-90-67, was a 54-year-old white woman in whom a diagnosis of carcinoma of the cervix was made on February 3, 1952. Treatment was carried out with x-ray and radium and again with radium when a recurrence was discovered in the vagina on August 14. On February 22, 1953 a vesicovaginal fistula 1 cm. in diameter was discovered as well as a rectal stricture admitting only the tip of the index finger. By September 24 this vesicovaginal fistula had increased in size and the patient was admitted for evaluation. She was found to have a hemoglobin of 66 per cent, a blood volume deficit of 1990 cc and evidence of weight loss. A urogram on October 14 revealed right hydronephrosis and evidence of pyelonephritis on the left side (fig. 3, *A*). She was operated upon on October 20. There was no evidence of recurrence in the abdomen. Both ureters were anastomosed to an isolated segment of ileum measuring approximately 12 inches in length. The postoperative course was stormy with temperature as high as 103F and clinical and laboratory evidence of hypopotassemia. She slowly recovered from this and at the time of discharge appeared to have a rather marked left hydronephrosis with diminished function and some evidence of dilatation on the right side. The most recent urogram reveals that both kidneys have returned to normal function although there is evidence of chronic pyelonephritis in the left kidney (fig. 3, *B*). She has been followed for 17 months and has gained 12–14 pounds in weight. The blood chemistry determinations are within normal limits. She has maintained her hemoglobin well and is very pleased with the ileostomy.

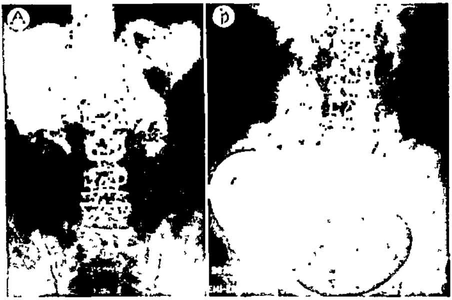

Fig. 3. Case 2. Right hydronephrosis. *A*, preoperative film *B*, recent urogram. Good function on both sides.

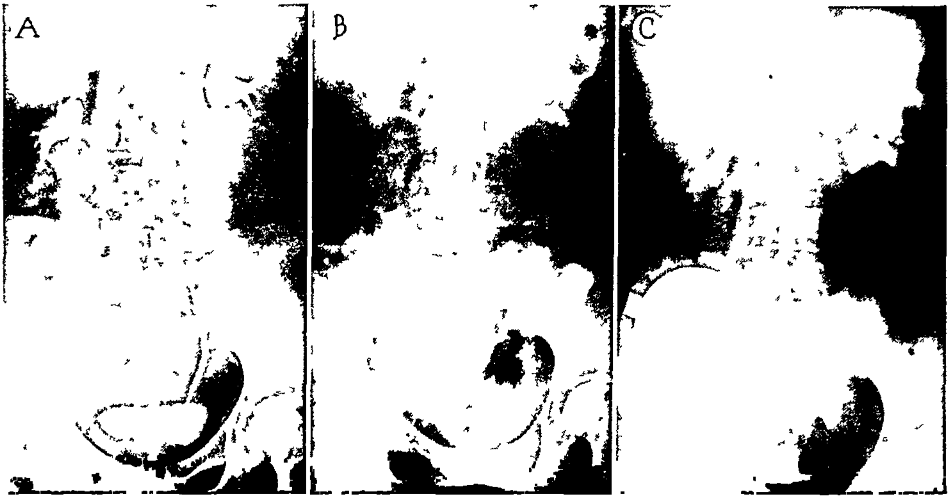

FIG. 4. Case 3. *A*, preoperative urogram. *B*, urogram during early convalescence while patient had mild hyperchloremic acidosis. Note hydronephrosis. *C*, normal urogram 1 year after ureteroileostomy. Normal serum electrolyte levels.

Case 3, M.M., University Hospital No. 01-93-47, was a 53-year-old white woman, in whom carcinoma of the cervix, stage 1, was diagnosed in February of 1952. She was treated with x-ray and radium. Her immediate post-treatment course was marked by a moderate irradiation cystitis. She was known to be a mild diabetic and was watched carefully for evidences of fistula. A rectovaginal fistula was found in March 1953. In April 1953 a loop-colostomy was performed because of the rectovaginal fistula. She was readmitted in January of 1954 with a vesicovaginal fistula, anemia and cachexia. The preoperative urogram is shown in figure 4, *A*. She was given a transfusion of whole blood and a high protein diet. On February 20 the abdomen was explored without finding any evidence of recurrent tumor. The right ureter was 1 cm. in diameter and when opened ejected purulent urine. Bilateral ureteroileostomy to an isolated segment 12 inches in length was performed. The postoperative course was smooth except for a slight tendency to hyperchloremic acidosis which was easily managed with Shohl's solution. Followup urograms (fig. 4, *B*) revealed hydronephrosis bilaterally which gradually improved and now at one year appear normal (fig. 4, *C*). She has maintained her hemoglobin well and manages her stoma without difficulty.

Case 4, N.W., University Hospital No. 02-52-70, was a 61-year-old woman in whom a diagnosis of carcinoma of the cervix, stage 1, was made in March 1951. She was treated by x-ray and radium. The patient was a diabetic of moderate severity. Marked proctitis developed during the next few months and on January 29, 1952 a diagnosis of rectovaginal fistula was made. In March 1952 a sigmoid colostomy was performed because of this. In February 1954 she was found to have a vesicovaginal fistula, and was admitted for evaluation. There was no evidence of recurrent tumor in the pelvis. A rectovesicovaginal fistula of rather large size was present. Urogram on March 15 revealed minimal bilateral hydronephrosis (fig. 5, *A*). She was operated upon March 30. There was no evidence of recurrent tumor in the abdomen. Bliateral ureteroileostomy was

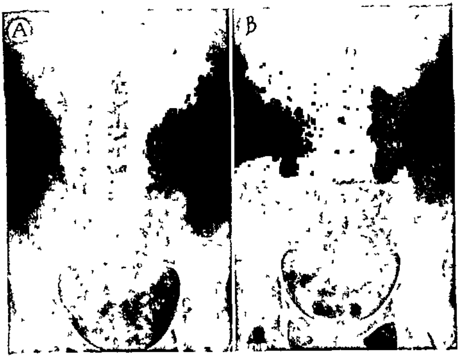

FIG. 5. Case 4. *A*, preoperative urogram. *B*, recent urogram.

performed. The isolated segment was 14 inches long. On the first postoperative day urine leaked around the ileostomy and urogram revealed hydronephrosis on both sides, with signs of peritoneal fluid. She was reoperated upon the second postoperative day. The anastomoses of both ureters to the ileum were found to be leaking and were resutured. Number 14 French Levine tubes were placed to drain the ureters extraperitoneally through proximal ureterotomy incisions. The apparent cause of the leakage was back pressure in the ileal segment due to plugging by mucus of a tube which has been placed in the ileal segment for drainage. The ureterostomy tubes were removed on April 16 and 17, and on April 28 she was discharged with the ileostomy functioning normally. This patient has been followed for 1 year and has done very well clinically. There have been no episodes of pyelonephritis and the most recent urogram shows no evidence of hydronephrosis (fig. 5, *B*). Her blood chemistry determinations have been within normal limits.

Case 5, M.A., was a 33-year-old woman, (PGH), No. 29-48-23, in whom a diagnosis was made of carcinoma of the cervix in 1950 and treated by irradiation. Fecal and urinary leakage were noticed from the vagina in 1951 and a vesicorectovaginal fistula diagnosed. The rectovaginal fistula was small and was managed by a constipation regimen. In 1953 cutaneous ureterostomies were performed at another hospital. She was admitted in December 1954 and was found to have good function bilaterally with early signs of chronic pyelonephritis (fig. 6, *A*). She complained of pain along the left ureter and pain on changing the tubes. There were strictures at the junction of skin and ureter bilaterally. The patient was threatening suicide because of her discomfort and urinary leakage about the tubes. Preoperative blood chemistry determinations showed a tendency toward hyperchloremic acidosis. At operation on January 19, 1955 the ureters were found to be greatly thickened and indurated and were separated with difficulty from the lateral peritoneal wall and skin. Ureteroileal anastomoses were completed, however, using a 14 inch segment of ileum. The postoperative course was smooth and at the time of discharge she was found to have a decreased CO_2 combining power, but a normal chloride level and approximately normal

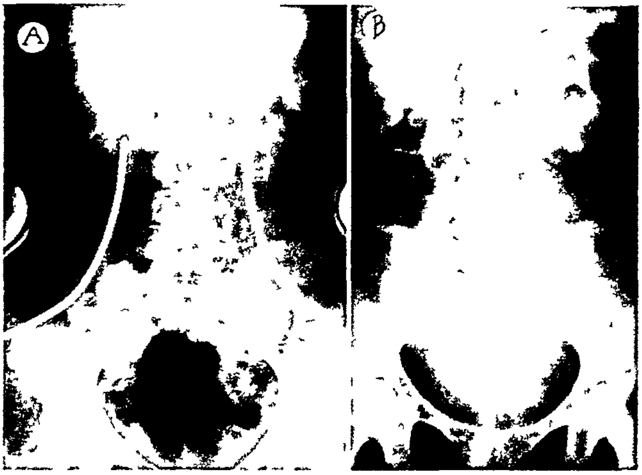

FIG 6 Case 5 *A*, preoperative urogram. Note minimal chronic pyelonephritis. *B*, urogram 3 months postoperatively.

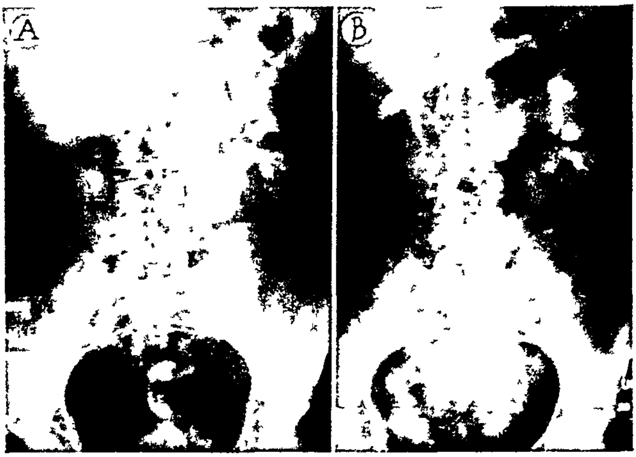

FIG 7 Case 6 *A*, preoperative urogram *B*, postoperative urogram. Minimal left hydronephrosis

serum sodium. She has been followed for a little over three months and has been doing well clinically without evidence of pyelonephritis. Her most recent urogram is shown in figure 6, *B*. From past experience this dilatation may be expected to diminish in the next 3 months.

Case 6, K.A., was a 39-year-old woman, (PGH), No. W2867. Carcinoma of the cervix was diagnosed in September 1952 and treated by irradiation. Severe proctitis and a rectovaginal fistula developed for which she had a colostomy in April 1953. Vesicovaginal fistula was diagnosed in June 1953. An attempt at plastic closure of this was made in March 1954 and this failed. She was admitted in February 1955 with a vesicovaginal fistula, colostomy in the left lower quadrant, and no evidence of recurrence or spread of her carcinoma of the cervix. Urogram revealed normal appearing upper tracts (fig. 7, *A*). Operation was done on February 23. The operative procedure was very difficult because of many adhesions but bilateral ureteroileostomy was accomplished. The isolated segment was 14 inches long. The postoperative course was uneventful. At the present time she has been followed for a little less than three months. The blood chem-

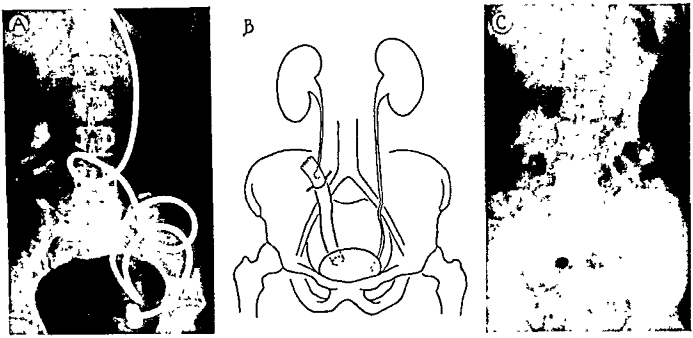

FIG. 8. M. H. *A*, preoperative urogram. Right hydronephrosis with calyceal calcification and nephrostomy. *B*, diagram showing ureteroileoneocystostomy. *C*, urogram 4 months postoperatively.

istry determinations have been within normal limits and her urogram is shown in figure 7, *B*. There is minimal dilatation of the left upper tract.

URETERAL INJURY

Injury of the ureter by irradiation therapy occurs much more frequently than is generally suspected. Careful and complete urologic investigation carried out in the course of long term followup studies in patients so treated for carcinoma of the cervix indicate an overall incidence of ureteral damage as high as 25 per cent. About 5 per cent are serious enough to require treatment.[1]

Transitory hydronephrosis is common early in the course of treatment. Late fibrosis and stricture are often asymptomatic and may be missed unless carefully sought. When such a case is discovered it is necessary to rule out recurrence or metastatic carcinoma for it is felt that only palliative treatment is indicated if carcinoma is found. In patients who appear to be free of carcinoma and have serious ureteral damage, the usual methods of management such as reimplantation and the Boari-Ockerblad procedure may be impossible because of the marked perivesical irradiation reaction and length of the damaged segment of ureter. Such a case was encountered in July 1953, and successfully managed by substituting a portion of ileum for the lower third of the ureter, as recommended by Baum.[7] The patient, M.H., University Hospital No. 00-40-42, was a 39-year-old woman who had received irradiation therapy for a stage 3 carcinoma of the cervix in 1950. Early in 1953 she was found to have right hydronephrosis, which was treated by intermittent ureteral catheterization by her attending gynecologist. In July 1953 right flank and abdominal pain developed and required a nephrostomy for relief. The patient was then lost from followup until January 1954 when she reappeared asking to be relieved of the nephrostomy. A urogram on January 8 revealed some improvement in the appearance of the right kidney but there appeared to be calcifications in several calyces (fig. 8, *A*). Her serum

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[7] Baum, W. C.: The clinical use of terminal ileum as a substitute ureter. J. Urol., **72**: 16-33. 1954.

electrolyte levels were within normal limits. On January 12 the right ureter was explored and found to be obliterated by a fibrous periureteritis from the bladder to well above the iliac vessels. A segment of ileum about 10 inches long was isolated and the proximal end closed. The ureter was divided above the narrowed area and anastomosed end-to-side to the ileum by means of the elliptical technique of Nesbit.[6] The distal end of the ileum was then anastomosed to the dome of the bladder by means of two suture layers of catgut. The ureteroileal anastomosis was placed retroperitoneally, but the ileoneocystostomy was intraperitoneal (fig. 8, *B*). Postoperatively there was some temporary slight leakage from the proximal anastomosis, which was attributed to obstruction of the bladder catheter with dilatation of the bladder and reflux up the ileum. Other than this her postoperative course was smooth, however, and the nephrostomy tube was removed on February 17. She was discharged soon thereafter. A urogram on June 3 revealed improvement in the appearance of the right kidney (fig. 8, *C*). She has been followed for approximately 16 months and has been clinically well. There has been no evidence of serum electrolyte disturbance.

DISCUSSION

The clinical course and pyelographic followup of all patients in whom a segment of ileum has been used as a urinary conduit have been very satisfactory. Except for one or two instances, where it was obviously due to technical difficulties or pre-existing disease, pyelonephritis has not occurred. Electrolyte disturbances have been minimal and in every instance apparently directly related to pre-existing renal damage, or to transient postoperative hydronephrosis. As Lapides has so well demonstrated, hyperchloremic acidosis after ureteroenterostomy is due to absorption of urinary constitutents in the presence of renal damage.[8] The fact that hyperchloremic acidosis was noted during the transient hydronephrosis in several cases and vanished when the drainage of the kidney improved confirms this. No patient has complained of anorexia or any other symptoms of electrolyte disturbance. All have been very satisfied with their ileostomy and find the adherent bag to be safe from leaks and easy to manage. Experience has been similar in ten additional patients in whom ureteroileostomy was carried out for other reasons.

SUMMARY

Vesicovaginal fistulas and ureteral strictures occurring as late complications of pelvic irradiation therapy are difficult to manage. Diversion of the urinary stream by anastomosis of the ureters to an isolated segment of small bowel with creation of an abdominal stoma for collection of urine has proven very satisfactory in 6 cases of vesicovaginal fistula. Substitution of a segment of ileum for the lower third of the ureter in a patient with ureteral damage due to irradiation therapy has also yielded satisfactory results.

The author is grateful to Dr. George Lewis and Dr. Michael Newton of the Gynecology Department, Hospital of the University of Pennsylvania, for their co-operation.

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[8] Lapides, J.: Mechanism of electrolyte imbalance following ureterosigmoid transplantation. Surg., Gynec. & Obst., **93:** 691–704, 1951.

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URINARY DIVERSION UTILIZING AN ISOLATED SEGMENT OF ILEUM

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For the past 2 years, an isolated segment of ileum has been used for conditions requiring urinary diversion. We were stimulated to adopt this procedure by personal observation of many cases of pelvic evisceration on which ileal bladder substitution had been done by Dr. E. M. Bricker. Our experience is now sufficiently great to warrant some conclusions concerning the value of the method.

The series consists of 41 cases, in thirty-five of which malignant disease was present, with no malignancy in six. Accurate followup has been obtained in all cases and we shall present an analysis of our results.

OPERATIVE MORTALITY

Four patients died before being discharged from the hospital. Three of these were extremely poor risks, and in retrospect, surgery should probably have been avoided. Advanced carcinoma was present and operation was done strictly for palliation because of severe bleeding and dysuria. Survival in this group was from three to six weeks and in no instance was the death directly due to the surgery. The fourth was definitely a postoperative death, on the sixth day following the operation. She was a diabetic who, after a fairly smooth convalescence, went into shock on the fifth day and died on the seventh. Findings were highly suggestive of micrococcic enteritis but this diagnosis was not confirmed at autopsy. As far as the ileal segment and the ureteral anastomosis were concerned, there was no abnormality. With a better selection of cases, our operative mortality of 9 per cent can be improved.

Complications. Principal complications are listed in table 1.

Urinary sepsis, as exemplified by chills and fever, was present in 12 patients (29 per cent). However, in a more detailed analysis, one finds that of these there were only three (7 per cent) in whom there was no definite reason for the sepsis. In two of the patients who died of extensive carcinoma, sepsis was present as a terminal phenomenon, in one there was a urinary leak, in another there was a right renal calculus with obstruction, in one there was a defective ileal stoma with urinary retention, and in four progressive hydronephrosis, either unilateral or bilateral, was present. Of the remaining 3 patients in whom no mechanical difficulty existed, sepsis has not presented any clinical problem. It has been mild in character, usually consisting of a single attack easily controlled by chemotherapy with no recurrence.

Progressive hydronephrosis was present in 7 patients (17 per cent). In three of these, the complication was corrected by reanastomosis of the ureter, with

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Read at annual meeting, American Urological Association, Los Angeles, Calif., May 18, 1955.

TABLE 1. *Complications*

	Cases	*Per cent*
Urinary sepsis	12	29*
Progressive hydronephrosis	7	17
Dermatitis from ileostomy bag	7	17
Wound dehiscence	4	9
Defective ileal stoma	4	9
Intestinal obstruction	3	7
Urine leak	2	5
Renal calculus	1	2
Fecal fistula	1	2

* In only 7% without obstructive uropathy or other obvious cause.

complete correction demonstrated by pyelographic followup. This favorable result emphasizes the importance of careful postoperative observation with the adoption of corrective procedures as soon as the difficulty is recognized. The balance of those patients with progressive hydronephrosis were terminal cases or in such poor condition that additional surgery was not indicated.

Dermatitis, either from sensitivity to the ileostomy bag or the paste used for its application to the abdomen, was encountered in 7 cases. Fortunately, in only two of these was true sensitivity to rubber present, and these certainly presented a distinct problem in management. In the other five, the dermatitis was the result of poor management by the patient in application of the bag. We were definitely at fault in not having given the patient more careful instruction prior to his leaving the hospital. Many of these people are in an older age group and are unable to devise proper management on their own initiative. However, for the most part, management of the ileostomy has presented very few difficulties. Patients seem to be quite satisfied with it and one hears fewer complaints than from the management of an ordinary colostomy.

Wound dehiscence occurred in 4 patients. This incidence is obviously too high and we are at a loss to explain its occurrence. All of the incisions were closed carefully; two of those that broke down had been closed with wire. Fortunately, there was no mortality in these 4 patients.

Defective ileal stoma, which occurred fairly early in 4 patients, was undoubtedly due to poor technique. In three of the four, the ileal segment was not brought through the muscle layers of the abdomen properly, and when the wound was closed, stenosis developed in that portion of the segment which was passing through the abdominal wall. In the fourth, repeated eversions of the stoma developed. In the process of construction, an unusually long segment of ileum was used and too wide an opening was made in the fascia of the abdominal wall. Both of these factors were no doubt contributory, and following shortening of the segment and revision of the opening in the abdominal wall, the patient has experienced no further difficulty.

Intestinal obstruction occurred early in 2 patients and late in a third. One must be very careful in establishing the ileal segment to utilize the portion of ileum as near to the ileocecal valve as possible and be sure that a pocket does not exist in the right gutter near the cecum.

Urine leak occurred in 2 patients. In one it was necessary to establish open drainage. Surprisingly enough no abnormality was found at the site of anastomosis and following drainage no further leakage occurred. The patient made an

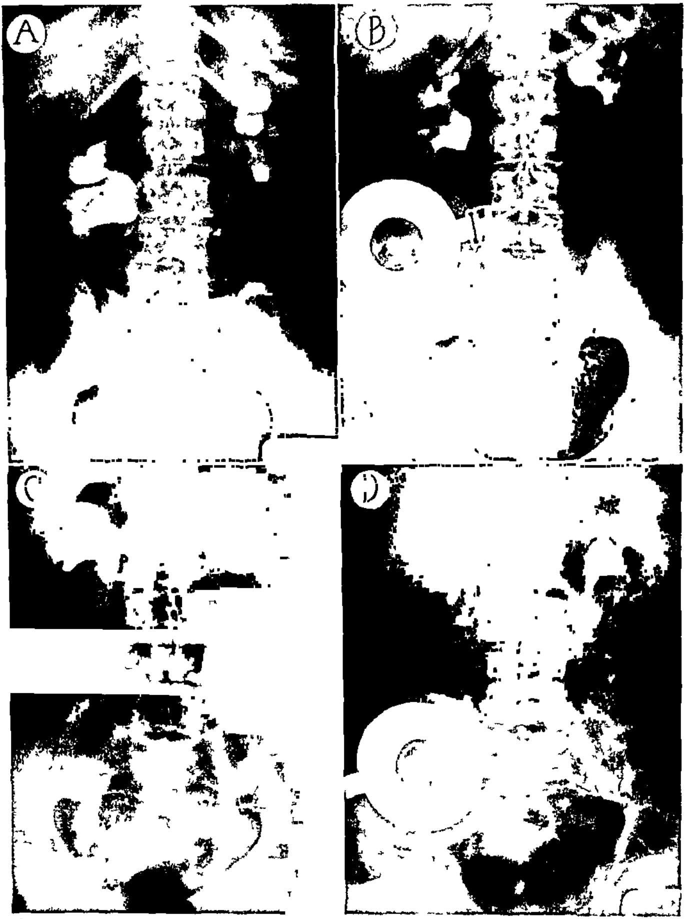

FIG 1 *A* and *B*, [illegible] idiation therapy for carcinoma of cervix, vesicovaginal fistula [illegible] preoperative, *B*, 6 weeks postoperatively *C* and *D*, 73-year c [illegible] sitional cell carcinoma of bladder, grade 2 Urinary frequency every 15 to 30 minutes day and night, or large doses of morphine, a hopeless invalid Completely rehabilitated after cystectomy, ileal bladder substitution Gained 40 pounds Working every day as a carpenter. *C* preoperative; *D*, 6 weeks postoperatively

uneventful recovery. In the second patient leakage developed through the abdominal incision on about the third postoperative day. This leakage persisted for approximately ten days and ceased spontaneously. End results in this patient were also satisfactory.

Renal calculus developed in one patient after 2 years. There was beginning hydronephrosis on the side in which the calculus developed The ureter has been reimplanted in the isolated segment and the calculus removed. One month later, the hydronephrosis had completely disappeared and the kidney had normal function on intravenous urography.

Fecal fistula occurred in one patient, secondary to a partial wound separation with strangulation of a section of small bowel in the incision. A secondary closure was required and the patient made an uneventful recovery.

Hyperchloremic acidosis has produced no problem either early or late.

PYELOGRAPHIC RESULTS

An overall total of seventy-three renal units were available for pyelographic followup. Of these, 50 units (68.6 per cent) were considered acceptable and twenty-three (31.4 per cent) unacceptable. No patient was considered acceptable in whom there was any hydronephrosis where none existed preoperatively, or in whom there had not occurred a marked improvement in pre-existing hydronephrosis. An analysis of the unacceptable group revealed these facts. Twelve units had pre-existing advanced obstructive disease which showed only partial improvement following transplantation into an ileal segment. No pre-existing obstructive renal disease was present in the other eleven unacceptable units.

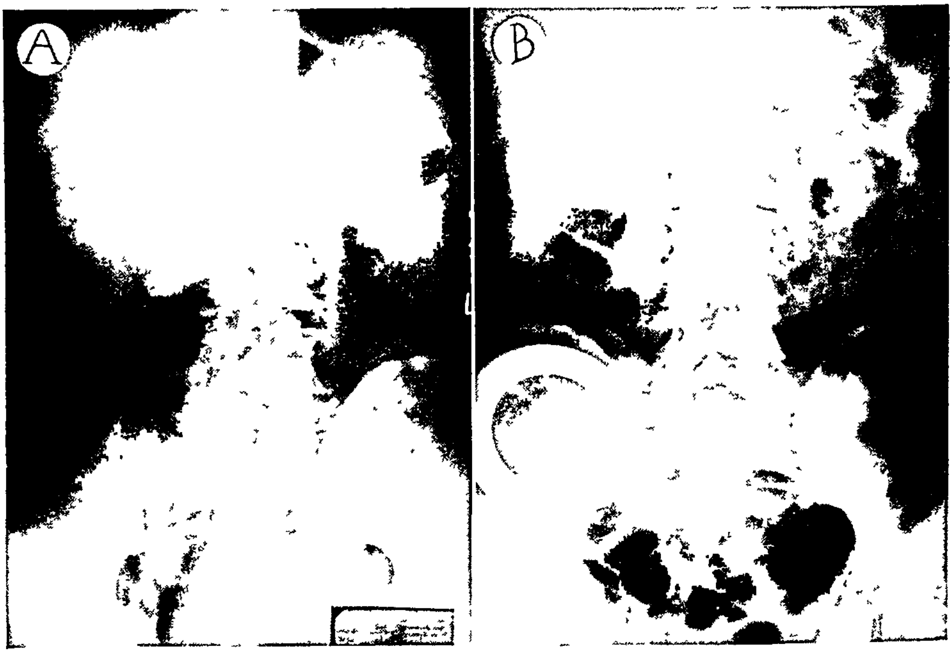

FIG. 2. Transitional cell carcinoma, grade 2, of urinary bladder. Cystectomy and ileal bladder substitution. Uneventful convalescence. *A*, preoperative; *B*, 4 months postoperatively.

From this latter group, three units have been corrected by re-operation and are now considered satisfactory If we eliminate those cases in which advanced renal disease existed prior to ileal bladder substitution, we find that 82 per cent are acceptable and 18 per cent unacceptable Although this 82 per cent figure is considerably better than that for most reported series following ureterosigmoidostomy, we believe that it is still too high and can be improved with more careful attention to the technique of the anastomosis

In order to further evaluate the prognosis as far as the upper urinary tract is concerned, we have studied each patient postoperatively with special reference to pyelonephritis, progressive hydronephrosis, or loss of renal function On this basis, we would consider that the overall renal prognosis was good in 23, fair in 4, and poor in 9 In 15 of the total group, the prognosis would have been considered poor prior to surgery Of these, improvement was sufficiently great in 7 to alter the renal prognosis to good Typical pyelograms from this group are shown in figures 1 and 2 In 5, there was a marked improvement both in the degree of upper tract dilatation and in renal function, but there still remained sufficient upper tract damage to warrant a prognosis of "poor" In 3 cases there was no improvement following transplantation into an ileal segment The prognosis was considered poor postoperatively in only 4 patients in whom it was considered good before ileal bladder substitition

DISCUSSION

From the foregoing study, it is our conclusion that the utilization of an isolated segment of ileum has a definite place in the field of urinary diversion Ureters with any degree of dilatation may be transplanted, with no fear of added early or late complications As a matter of fact, a slight degree of dilatation seems to facilitate the ease with which transplantation can be accomplished When we have endeavored to transplant widely dilated ureters into the rectosigmoid, we have invariably encountered early and late complications of sufficient severity to contraindicate the procedure Since hydronephrosis and hydroureter are fairly frequent complications of carcinoma of the urinary bladder, the utilization of an isolated ileal segment would seem to present a distinct advantage in those cases in which this complication exists

This operation is a highly technical one, and one in which mechanical errors carry a severe penalty Meticulous attention to minor details is essential if the operation is to succeed Since it is frequently done following cystectomy, when the surgeon is already fatigued, we believe that there may be some advantage in utilizing two operators for the overall procedure, the one performing the cystectomy, and the other, the ileal bladder substitution

We should also like to emphasize the necessity for regular periodic examinations following operation Patients with urinary diversion of any sort cannot be considered as normal individuals However, many complications of a serious nature may be completely avoided or corrected satisfactorily if recognized early Therefore, it is essential that these people be observed at intervals not to exceed 3 months for the first year and at increasing intervals thereafter Adoption of this regimen will add materially to the practicability of the procedure

SUMMARY

A series of 41 cases in which an isolated loop of ileum has been utilized for urinary diversion is presented. There was an operative mortality of 9 per cent. Principal postoperative complications consisted of urinary sepsis, progressive hydronephrosis, wound dehiscence, defective ileal stoma, and dermatitis. Of a total of 73 units analyzed pyelographically, 68.6 per cent were considered acceptable and 31.4 per cent unacceptable. Eliminating those cases in which advanced renal disease existed prior to operation, 82 per cent were considered acceptable and 18 per cent unacceptable.

We have found urinary diversion with the isolated ileal loop a valuable procedure. For the present, we propose to utilize this method in all cases on nonmalignant disease, in children, and in those cases of carcinoma of the urinary bladder where an above average prognosis is anticipated. We shall continue to use ureterosigmoidostomy in most cases of carcinoma of the urinary bladder, except those in which ureteral dilatation is present prior to surgery. Although results appear promising, final judgment must be reserved until long term followup studies are available.

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A PATHOLOGICAL STUDY OF URETEROVESICAL JUNCTIONS OF TWO STILLBORN INFANTS WITH COMPLETE URETHRAL ATRESIA

JOHN A HUTCH

The urinary tracts of two stillborn infants serve as the basis of this report In each case the entire urinary tract including the penis and urethra was removed at the time of postmortem examination The same pathological features were present in both specimens and consisted of complete urethral atresia plus polycystic kidney disease Associated with the urethral atresia is severe bladder trabeculation, hydroureter and hydronephrosis While this group of pathologic changes is unusual enough to warrant attention, the purpose of this paper is not to enlarge on the embryology of the situation, but rather to discuss certain pathological changes observed at the ureterovesical junction

Figure 1 shows the two specimens in total The basic pathological change is the same in both and is characterized by bilateral polycystic kidney lesions plus complete atresia of the urethra Associated with this is severe bladder trabeculation, hydroureter and hydronephrosis In the specimen on the left the right kidney is infantile Also notice in the specimen on the right that the saccule at the ureterovesical junction has been dissected out Figure 4, *C* shows this area in closeup

In figure 2, *A* the tremendously dilated ureter in the specimen on the left (fig 1) has been opened The picture was taken looking caudally at the ureterovesical junction from within the ureter The ureteral side of the saccule is clearly demonstrated in the center of the picture The ureteral catheter is in the ureteral orifice which lies on the undersurface of the saccule The bladder is seen at the lower left corner One can see quite plainly that the saccule is largely extravesical This point will be emphasized in figure 2, *C* Figure 2, *B* is an artist's illustration of this

Figure 2, *C* is another view of the ureterovesical junction depicted in figure 2, *A* It is designed to show the extent of the extravesical part of the saccule The ureter has been cut away so that the dome of the saccule can be seen The ureteral catheter is in the intravesical orifice The thick walled, trabeculated bladder may be seen on the left The opened, dilated ureter extends to the upper right As this bladder strained to rid itself of its contents against a complete obstruction the bladder musculature must have pulled away from the intravesical ureter and created a defect through which the bladder mucosa herniated to produce the saccule shown here The intravesical ureter thus robbed of its normally supporting tissue is pulled into an extravesical position along the floor of the saccule Figure 2, *D* is an artist's illustration of this

Figure 3 is a photomicrograph which shows a longitudinal section of the bladder wall, saccule and lower ureter at a very low power Study shows that the bladder wall in the region of the ureterovesical junction has been widely pulled apart to

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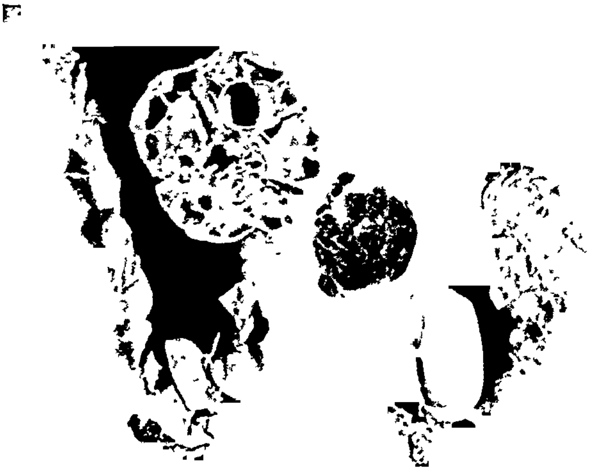

FIG. 1

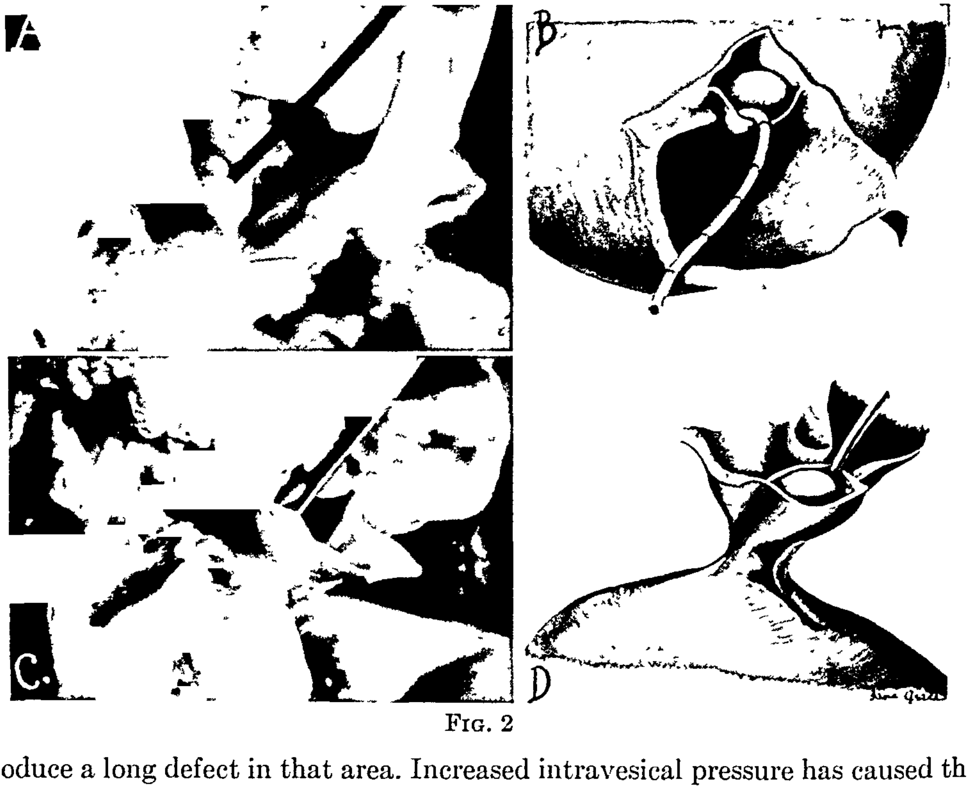

FIG. 2

produce a long defect in that area. Increased intravesical pressure has caused the bladder mucosa to herniate through the defect and produce a saccule or diverticulum. The saccule or diverticulum has literally herniated into the lower ureter. One also observes that the ureteral orifice and the intravesical ureter have dropped into an aberrant position on the floor of the diverticulum. This photomicrograph also shows that the ureteral orifice and the intravesical ureter which normally lie within the bladder now lie in a position well outside of the bladder.

Figure 4, *A* is a close up of the specimen on the right in figure 1. It is included to show the gross appearance of the ureter as it merges with the bladder. The

FIG. 3

presence of a saccule could scarcely be suspected because it is confined within the fascia of the ureter. It is easy to see how this saccule can be overlooked unless searched for specifically.

In figure 4, *B*, which is the same ureter illustrated in figure 4, *A*, the saccule has been made to stand out by passing the tip of a Mayo clamp into it from within the bladder.

Figure 4, *C* shows the appearance of the same ureter as illustrated in figure 4, *A* and *B* after the saccule has been dissected out. The bladder is on the left. The ureter, with a probe in it, is seen emerging from the bladder under the saccule. It is interesting that the dilation of the ureter does not begin at its junction with the bladder but rather at a point 2 to 3 centimeters above the bladder. It is my belief that the undilated segment of the ureter is that part which normally lies within the bladder (intravesical ureter). As the bladder strained to empty its contents, the detrusor muscles were literally pulled away from the ureter resulting in a weakness in the bladder wall through which the bladder mucosa herniated to produce the saccule we see. As the bladder musculature which normally supports the intravesical ureter was pulled away from this structure, it fell into an extravesical position as we see it here. The ureter then began to dilate, not at the ureteral orifice but at the junction of the intra- and extravesical ureter. Figure 5, *A* is an artist's illustration of this area. Figure 5, *B* is an artist's illustration of the cystoscopic appearance of this ureteral orifice. Note the lateral border of the trigone as it disappears into the saccule. The ureteral orifice cannot be seen cystoscopically because it lies deep within the saccule.

Figure 6 is a photomicrograph of the ureteral orifice of the specimen on the right in figure 1. This saccule has been carefully dissected out before it was sectioned. This illustrates very clearly the defect in the bladder wall and the

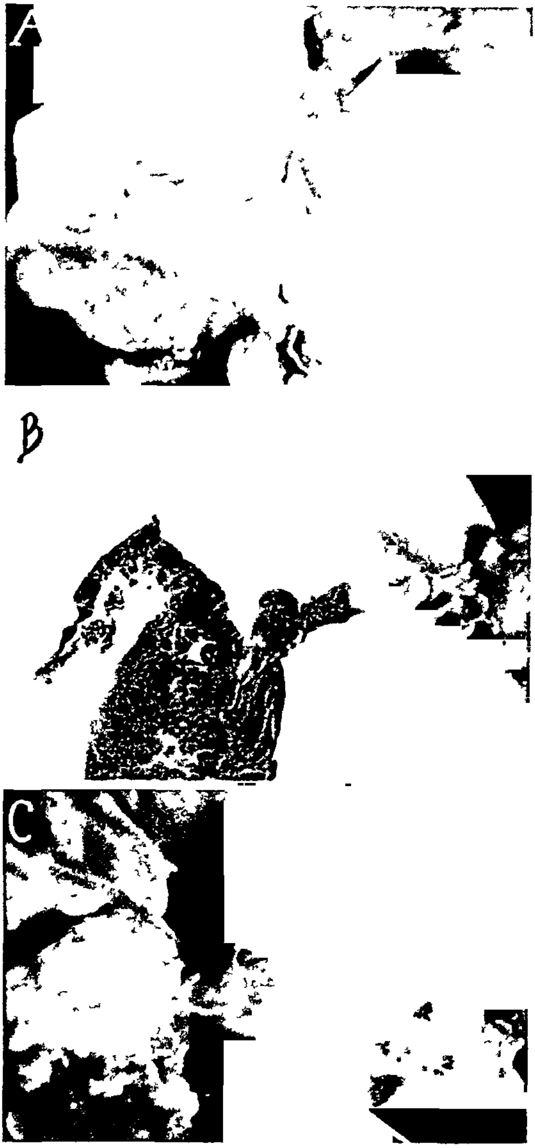

FIG. 4

resultant diverticulum. It also shows the ureteral orifice on the floor of the diverticulum and in a distinctly extravesical position. In spite of the great dilatation of the ureter above, neither the ureteral orifice nor the intravesical ureter is involved in this dilatation

X-RAY CHANGES CAUSED BY DEFECT

In the hope that a familiarity with the x-ray pattern caused by these changes at the ureterovesical junction would aid us in recognizing this entity clinically, the following x-ray pictures were made:

Figure 7 shows the specimen illustrated on the right in figure 1 after the bladder had been filled with 20 per cent skiodan. Note the bilateral "dog ears" at the ureterovesical junctions produced by the contrast medium filling the saccules.

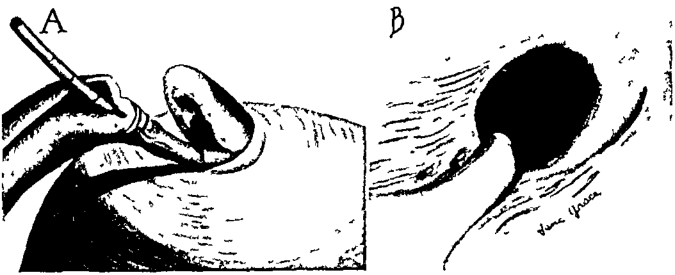

Fig. 5

Fig 6

Fig 7

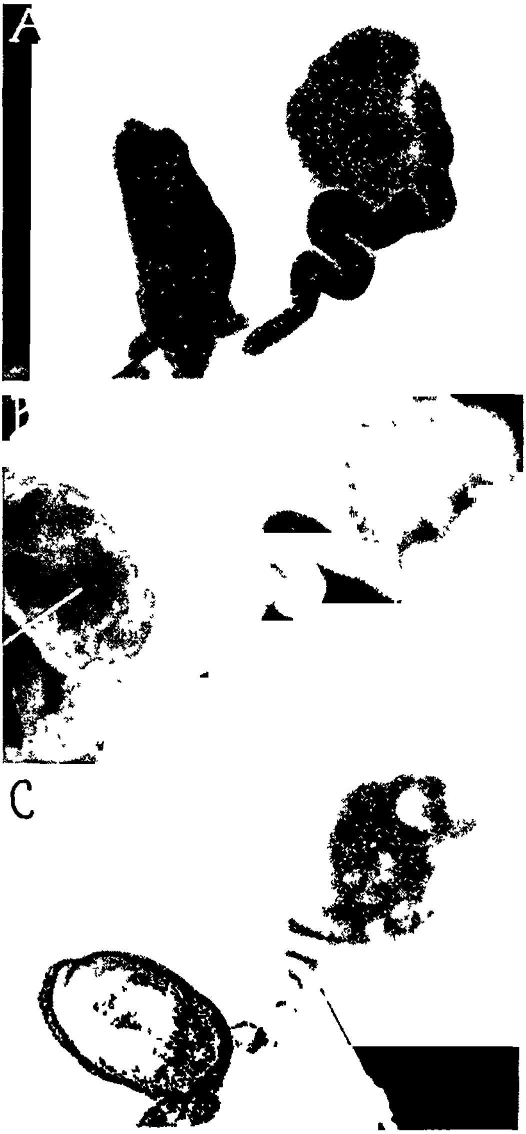

FIG. 8

Figure 8, *A* is the same specimen with 20 per cent skiodan in the bladder and in the left ureter. The arrow points to the "notch sign" or "ureteral gap" which is a negative filling defect in the ureter caused by the saccule.

Figure 8, *B* is the same specimen. This time, however, the bladder is filled with air and the left ureter with skiodan. Note the clear demarcation between the saccule and the dilated ureter. It is also interesting that none of the skiodan injected into the ureter escaped into the bladder, although it was injected under considerable pressure. This is in spite of the fact that there was no obstruction in the lower ureter to the passage of a 6F ureteral catheter.

Figure 8, *C* is the same specimen with both the bladder and the left ureter filled with air. Note that the wall of the saccule is thicker than the wall of the ureter. Also, notice the trabeculation in the bladder.

DISCUSSION

Ureteral orifices engulfed in saccules or diverticula are observed frequently They occur in the bladders of patients with prostatic hypertrophy, congenital bladder neck obstructions, urethral valves or strictures They are also seen in the bladders of paraplegic patients with hypertonic neurogenic bladders In each of these conditions the bladder is trabeculated and the formation of the saccule is probably part of the trabeculation process As the bladder wall is called upon to contract vigorously either to empty its contents against an obstruction or because of spastic nervous impulses reaching it from the spinal cord, the smooth muscle fibers of the bladder wall regroup themselves into trabecular bundles and pull away from the intramural ureter, thus producing a defect in the bladder wall at the ureterovesical junction *

Through this defect the bladder mucosa herniates, pulling the intravesical ureter and ureteral orifice into the depth of the saccule thus created In such a pathological position the intravesical ureter has lost the support normally given it by the bladder wall and its function becomes impaired so that reflux may occur or a functional partial obstruction develops in the intravesical ureter, or both Either of these conditions alone or both acting together could result in dilatation of the upper urinary tract

To get a true concept of the ureterovesical junction, one must not think of it as a simple tube but rather as a combined structure consisting of ureter and of bladder wall Functionally the intravesical ureter is dependent upon the maintenance of its normal anatomical relationship with that part of the bladder wall through which it passes We have learned to recognize these conditions in which the lumen of the intravesical ureter is organically obstructed (stones, tumor, tuberculosis and on a congenital basis, ureterocele) More perplexing have been those cases in which our x rays indicate an obstruction at the ureterovesical junction yet cystoscopically our catheters pass through this apparently obstructed segment of ureter with no difficulty In these cases we must cast our attention from the ureter *per se* to the bladder wall and to the subtle relationship between the ureter and the bladder wall through which it passes

Any discussion of the mechanisms by which this defect causes dilatation of the upper urinary tract is conjecture The association of this defect with hydroureter and reflux in cord injury cases is highly consistent In reviewing 8 cases of paraplegia in which the dilatation of the upper urinary tract was so severe that the patients died in uremia or required nephrostomy drainage to maintain life, distinct saccules were present in all of the 15 ureters involved In less severe cases the presence of the saccule is still highly consistent but some cases will be found in which early dilatation or reflux is present before a definite saccule can be demonstrated. Similarly, one may occasionally find a well defined saccule with a good upper urinary tract about it. This, however, is not common. All in all, the association of this saccule engulfing the ureteral orifice with reflux and or hydroureter is highly consistent.

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* The smooth muscle bundles which make up the bladder wall originate in the prostatic capsule, encircle the bladder and insert on the opposite side of the prostatic capsule (Gray's Anatomy, Lewis W H, pp 1252, 24th ed) When they contract or shorten, they empty the contents of the bladder and at the same time enlarge the bladder neck Chronic dilatation of the bladder neck is a frequent finding in paraplegic patients with upper motor neuron lesions This is probably also true in the patient with prostatic hypertrophy but it is impossible to be certain as the bladder neck is filled with hypertrophied prostatic tissue If we visualize the bladder as a hollow muscular ball perforated by three apertures (one urethral and two ureteral) and we know that severe trabeculation enlarges one of these holes, it is not unreasonable to believe that all three holes are enlarged, thus producing the defect at the ureterovesical junction in the 2 cases presented here

The intravesical ureter has two functions: one is to prevent the reflux of bladder urine; the other is to allow ureteral urine to pass unobstructed into the bladder. Considering each of these separately we find that the intravesical ureter is ideally adapted to the prevention of reflux. It is a thin walled collapsible tube passing obliquely through the bladder wall. As it contains no circular muscle fibers, its only muscular activity is that of shortening or lengthening. During the resting stage, it is passively collapsed between the intravesical pressure above and the bladder wall behind. In its intramural position it is probably kept closed by the bladder muscles which surround it. The ureteral fluid propelled by the peristaltic wave down the ureter seems to have adequate force to pass through this valve without difficulty. The intravesical ureter does not participate actively in the passage of urine through it* (at least it exerts no muscular activity during this phase when studied cystoscopically). The intravesical ureter goes into action at the very end of the spurt of urine. It shortens and pulls the ureteral orifice sharply upward. This activity closes the intravesical ureter tightly either by pulling its walls together primarily or by bending its collapsible length over the bladder muscles which lie under it or, as probably happens, both. The intravesical ureter then drops back slowly to its resting position to await the next spurt of urine. Loss of the support of the bladder muscles which normally surround it may impair the function of the intravesical ureter to such a degree that it can no longer prevent reflux.[1]

The second function of the ureterovesical junction is to aid, or at least not hinder, the flow of ureteral urine into the bladder. It is more difficult to demonstrate that this defect at the ureterovesical junction actually serves as an obstruction in the ureter. Some have argued that it is unnecessary to labor this point at all because the reflux alone could account for the dilatation of the upper urinary tract. There are many cases in which reflux cannot be demonstrated in which the ureter is greatly dilated and apparently from a functional obstruction of the ureterovesical junction. There are also many cases where the emptying of the ureter is greatly delayed even though the bladder is drained to rule out reflux as a cause of this delay. It is very possible that such an intravesical ureter deprived of its normal support from the bladder wall acts as a partially obstructing segment in the ureter. While the exact reason for this is not known, some possibilities include the following. As the intravesical ureter loses its bladder support, it drops into the extravesical space and becomes a segment of the extravesical ureter which, as it has no circular fibers, cannot convey the peristaltic wave efficiently A second possibility is that as the intravesical ureter loses the support of the bladder wall, it is too thin and collapsible to accommodate the advancing waves of urine without buckling, thus serving as a partial obstruction A third possibility to consider is suggested by the microphotographs of the cases presented As the saccule enlarges, it herniates along the ureter and within the fascia of the ureter It could partially obstruct the intravesical ureter by external pressure This is probably not the case, however, as hydroureter may begin before the saccule is large enough to obstruct Also, in conditions like the lower motor neuron bladder and megalobladder, the ureter dilates even when no saccule is present[2]

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* Cystoscopically, we see no peristalsis in the intravesical ureter. This is as expected as the intravesical ureter has no circular fibers.

[1] Hutch, J. A.: Vesico-ureteral reflux in paraplegia. J. Urol., **68:** 457, 1952.

The exact point at which the ureter begins to dilate is of interest It has been suggested that this occurs at the junction of the intravesical and extravesical ureter A glance at the photomicrographs shows that the ureteral orifice is not dilated even though the ureter is greatly dilated The dilatation must begin at some point above the orifice Since the role of the intravesical ureter is a passive one as far as conveying ureteral urine into the bladder is concerned, it would not be expected to dilate in the face of a functional obstruction in the lower ureter It would be under no increased work load because emptying the ureter is not its job If the ideas expressed above are correct, the intravesical ureter (deprived of its supporting bladder muscle) is the actual obstruction and one would expect the ureter to begin to dilate above it

SUMMARY

Two cases, both stillborn infants, are presented In each case the basic lesion is complete urethral atresia associated with polycystic kidney disease Secondary to the urethral stenosis is bladder trabeculation, hydroureter and hydronephrosis A detailed study of the ureterovesical junction is made in both specimens A herniation of the bladder mucosa through a defect in the bladder wall at the point where the bladder is pierced by the ureter is demonstrated It is also shown that the intravesical ureter has been carried into this herniation

The discussion deals with the development of the saccule and with the upper urinary tract changes which are so often associated with this saccule

I wish to thank Dr Edward J Richardson and Dr Melvin Friedman for bringing these cases to my attention I also wish to thank Mrs Jane Grace for the artist's illustrations of this material

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CARCINOMA OF THE PROSTATE GLAND: 5-YEAR SURVIVAL FOLLOWING ANTIANDROGENIC TREATMENT

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Fourteen years have now elapsed since Huggins and his co-workers established the basic concepts governing endocrine treatment of advanced prostatic carcinoma. It was, therefore, considered timely to review a series of clinical records of patients admitted to the urological service because of this disease and to study the ultimate course of these patients with the hope of learning something about factors that influence the 5-year survival rate.

The clinical records of 205 patients all treated between July 22, 1941 and April 1, 1950 on the urological service of the Massachusetts General Hospital were carefully examined. In addition, 16 patients treated on the private service between 1947 and 1950 were included in the study, making the total series 221 patients. All of these patients were treated by bilateral orchiectomy and estrogens or estrogens alone. Special attention was paid in this study to the following points: rectal examinations, particularly with reference to the prostate gland; serum acid phosphatase level; the condition of the upper urinary tracts by pyelography; the presence or absence of bone metastasis; and final duration of survival. A 5-year followup was obtained in all but 4 patients. These 4 patients were considered in the series as non 5-year survivors.

"Advanced" carcinoma may be defined as a malignant lesion of the prostate gland, which, on examination, gives evidence of extracapsular extension, whether locally in the pelvis, as determined by rectal palpation, or peripherally in the lymph nodes or bones, as demonstrable by x-ray examination. In the absence of obvious distant lymphatic or osseous metastases, the local lesion was always too extensive to warrant an attempt at complete surgical extirpation by radical prostatectomy. This is the group which, the literature states again and again, comprises from 90 to 95 per cent of all prostatic carcinomas encountered in most clinics.

Diagnosis in the vast majority (84 per cent) of these cases was confirmed histologically by microscopic examination of tissue removed either by transurethral prostatic resection or Silverman needle biopsy through the perineum. In the 16 per cent without histological confirmation, there was no doubt by the clinical examination and subsequent course of the patient that this disease was present. No case of occult carcinoma, found incidentally after simple enucleation, was included in this analysis.

These cases were divided into three groups (table 1).

Group A, 139 patients treated by "immediate" orchiectomy and estrogenic hormone: In this group orchiectomy was performed as soon as the diagnosis of prostatic carcinoma was made. The patient was then started on stilbestrol in

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Read at annual meeting, American Urological Association, Los Angeles, Calif. May 19, 1955.

TABLE I

Group	Treatment	Number of Patients
A	"Immediate" orchiectomy and estrogens	139
B	*"Late" orchiectomy and estrogens*	48
C	Estrogens alone	34
	Total series	221

TABLE 2 *Comparison of 5 year survival, "early" and "late" orchiectomy series*

	Without Bone Metastasis	With Bone Metastasis
Group A 139 patients	90 patients 7 died of unassociated disease 38 patients survived 5 or more yrs *5 Year Survival—45 7%*	49 patients 2 died of unassociated disease 6 patients survived 5 or more yrs *5 Year Survival—12 7%*
Group B 48 patients	37 patients 5 died of unassociated disease 15 patients survived 5 or more yrs *5 Year Survival—46 8%*	11 patients 1 patient survived 5 or more yrs *5 Year Survival—9 1%*
A & B (combined series) 187 patients	127 patients 12 died of unassociated disease 53 patients survived 5 or more yrs *5 Year Survival—46 1%*	60 patients 2 died of unassociated disease 7 patients survived 5 or more yrs *5 Year Survival—12 1%*
Nesbit & Baum 1950	43 6% (78 patients)	20% (35 patients)

dosage that varied from 1 to 10 mg daily and usually averaged 5 mg daily The survival was calculated from the date of performance of the orchiectomy and not from the onset of symptoms as given in the patient's history The only additional surgical therapy was transurethral resection for bladder neck obstruction when indicated

Group B, 48 patients treated by "late" orchiectomy and estrogenic hormone The treatment consisted of estrogenic hormone, usually stilbestrol, 5 mg daily for varying periods of time from 6 months to 4 years, followed by orchiectomy In other words, orchiectomy was delayed from 6 months to 4 years, sometimes because the patient refused the operation or sometimes because orchiectomy was not urged In over one third, the period of delay in instituting orchiectomy was 2 years or longer The survival was calculated from the time when the estrogenic hormone therapy was begun Invariably the estrogenic hormone was continued after orchiectomy Whenever bladder neck obstruction occurred, transurethral prostatic resection was carried out

TABLE 3. *Comparison of 5-year survival. Patients without bone metastasis*

	% 5-Year Survival	Nesbit & Baum 1950
Orchiectomy & estrogens (127 patients)	46.1%	43.6 % (78 patients)
Estrogens alone (30 patients)	26.6%	29% (63 patients)

TABLE 4. *Observations on clinically controlled groups*

44 patients showing: 1) normal serum acid phosphatase level, 2) no hydronephrosis, 3) no demonstrable bone metastasis

7 patients died of unassociated disease

22 patients survived 5 or more years

5-Year Survival—59.4%

Group C, 34 patients: In this group treatment consisted of estrogenic hormone alone without orchiectomy. Survival was calculated from the time of onset of estrogenic therapy. Here too, whenever bladder neck obstruction occurred, transurethral resection was performed.

In evaluating the 5-year survivals in groups A and B, it becomes apparent (table 2) that there was no significant difference in the 5-year figures. Therefore, these 2 groups were combined into a series of 187 patients treated by orchiectomy and stilbestrol, plus transurethral resection, when indicated, for the relief of bladder neck obstruction.

The influence of bone metastases on 5-year survival is also demonstrated in table 2. These observations are based on a study of 187 patients. Sixty or 32 per cent of the entire group of the patients had bone metastases demonstrable at the time of the initial examination. Here the 5-year survival rate is 12.1 per cent (compared to Nesbit's figure of 20 per cent). In contrast with this, is the figure for 5-year survival in 127 patients without bone metastases—46.1 per cent, a figure comparable with that of Nesbit and Baum (1950), 43.6 per cent.

These figures are to be compared with the group of 30 patients without bone metastases treated by stilbestrol alone. See table 3. The 5-year survival figure here is 26.6 per cent which shows the superiority of orchiectomy and stilbestrol treatment over stilbestrol alone. Nesbit's figure here is 29 per cent. As to the group with metastases, treated by stilbestrol alone, the series is too small for adequate statistical analysis, there being only 4 patients, one of whom survived 5 years.

Attention was then directed to the study of clinically controlled series (table 4). This table lists the data on 44 patients in whom the following clinical criteria were satisfied at the time of the initial examination.

1) The serum acid phosphatase was 3.0 or less Gutman units.
2) The upper urinary tracts were normal.
3) No bone metastases were demonstrable.

Here, the most favorable group, the 5-year survival rate was 59.4 per cent.

In marked contrast was the group of patients who had, at the time of initial examination:

1) Elevated serum acid phosphatase, 3.1 or more Gutman units.

TABLE 5 *Influence of hydronephrosis on 5 year survival*

119 Patients without Bone Metastasis

With Hydronephrosis (38 Patients)	Without Hydronephrosis (80 Patients)
2 died of unassociated disease	10 died of unassociated disease
12 survived 5 or more years	38 survived 5 or more years
5 Year Survival—32 4%	*5 Year Survival—54 3%*

TABLE 6 *Influence of elevated serum acid phosphatase level on 5 year survival*

104 Patients without Bone Metastasis

With High Acid Phosphatase (33 Patients)	With Normal Acid Phosphatase (71 Patients)
1 died of unassociated disease	7 died of unassociated disease
9 survived 5 or more years	30 survived 5 or more years
5 Year Survival—31%	*5 Year Survival—46 8%*

2) Unilateral or bilateral hydronephrosis
3) Demonstrable bone metastases

The series here was small, 11 patients, with no 5-year survivals This group had the poorest prognosis

The influence of hydronephrosis was then investigated Table 5 shows the results in 119 patients without bone metastases These were subdivided into 39 with hydronephrosis and 80 without hydronephrosis Among the 39 with hydronephrosis, 32 4 per cent survived 5 years, whereas, 54 3 per cent of those without hydronephrosis survived 5 years

A similar observation is made in table 6 in regard to the influence of an elevated serum acid phosphatase on 5-year survivorship

This was studied in 104 patients, 33 of whom had an elevated acid phosphatase and 71 of whom had a normal acid phosphatase level Among the elevated acid phosphatase group, the 5-year survivorship was 31 per cent against 46 8 per cent among the group with normal acid phosphatase

CONCLUSIONS

When a patient with extensive local malignant disease of the prostate, too extensive for radical prostatectomy, has a normal upper urinary tract as determined by excretory urography, a normal serum acid phosphatase level and no demonstrable bone metastases, he has a 59 per cent chance of living 5 years if he is treated with orchiectomy and stilbestrol and if his vesical neck obstruction is relieved by transurethral resection, provided that he survives unassociated diseases

If such a patient has hydronephrosis or elevated serum acid phosphatase without demonstrable bone metastases and is treated in the same manner, his chance for 5-year survival falls to about 31 or 32 per cent

If, in addition to hydronephrosis and an elevated serum acid phosphatase, he has bone metastases, his chance for 5-year survival approaches 0 per cent

In this series, as far as 5-year survival is concerned, orchiectomy and stilbestrol treatment proved superior to stilbestrol alone in the group that showed no demonstrable bone metastases.

This study suggests that an adequate evaluation of newer treatment methods, such as radioactive isotopes, for example, must require precise definition of the group of patients treated, in terms not only of the presence or absence of bony metastases, but also the serum acid phosphatase level and the condition of the upper urinary tract in order to insure fair comparison with results obtained by existing antiandrogenic methods of treatment.

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THE EFFECTS OF PROSTATIC SURGERY ON THE LEVEL OF SERUM ACID GLYCEROPHOSPHATASE

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Soon after determinations of serum acid phosphatase came into general use in the diagnosis of prostatic carcinoma, it became evident that prostatic acid phosphatase might enter the circulation after trauma, even of the noncancerous gland This possibility was mentioned by Woodard and Dean[1] in 1947 Transitory elevations in the serum acid phosphatase after prostatic massage have been reported [2] In one case, Daniel and Van Zyl[3] were able to show that the expression of 0 3 cc of prostatic cyst fluid into the circulation could theoretically account for the rise observed in the serum acid phosphatase following massage of the prostate More recently Fishman and co workers[4, 5] have studied the elevation in serum "prostatic" acid phosphatase following prostatic massage, making use of the L tartrate inhibition of the "prostatic" fraction of the total serum acid phosphatase to demonstrate that such elevations are due to the appearance of "prostatic" acid phosphatase in the circulation, apparently as a result of the manipulation Elevations of serum acid phosphatase to thirty to forty times the normal level have been reported after localized infarction of a benignly enlarged prostate [6] In view of evidence that trauma may cause prostatic acid phosphatase to enter the circulation, it seemed desirable to determine the incidence and extent of this process during prostatic surgery

METHODS AND MATERIAL

The acid phosphatase activities of serum and tissue were determined by the methods previously described by one of us [7] The substrate employed was sodium beta glycerophosphate Inhibitors were not used Normal values for serum acid phosphatase range from 0 1 to 0 9 units per 100 cc, values above 0 7 units per 100 cc being uncommon The range of acid phosphatase activity in prostatic tissue is very wide, but usually falls between 100 and 1000 units per gram of tissue

The clinical material was drawn in random fashion from patients with benign

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TABLE 1. *Effect of prostatic surgery on serum acid phosphatase*

Case Number	Patient	Age	Prostatic Diagnosis	Nature of Surgery	Time Relative to Maximal Trauma	Serum Acid Phosphatase Units/ 100 cc.	Tissue Acid Phosphatase Units/ gm.	Anesthesia	Significant Elevation
1	R. S.	65	Carcinoma	Perineal implantation of radon seeds	61 days before 60 days before Immediately after 7 days after 110 days after	0.89 0.82 1.9 0.71 0.86		Local	Yes
2	A. B.	52	Carcinoma	Difficult inguinal lymph node biopsy	22 days before 3 days before Immediately before Immediately after 4 days after	89.0 28.8 68.4 72.8 43.7	24	Local	No
3	J. G.	68	Clinically carcinoma	Aspiration biopsy	1 day before 1 day before Immediately before Immediately after 17 days after	1.7 2.2 1.8 1.5 1.7		Local	No
4	B. C.	73	Benign hyperplasia	Suprapubic prostatectomy	7 days before Maximal trauma 8 days after	0.29 3.0 0.62		Spinal	Yes
5	S. W.	57	Benign hyperplasia	Suprapubic prostatectomy	Immediately before Immediately after	0.76 3.1	1350 1530	General (sodium pent.)	Yes
6	A. G.	56	Benign hyperplasia	Perineal biopsy of prostate	2 days before Immediately after	0.29 0.48		General (sodium pent. and ether)	No
7	D. L.	66	Benign hyperplasia	Perineal biopsy of prostate	14 days before Maximal trauma	0.47 0.13		General (sodium pent. and nitrous oxide)	No

8	M Z	54	Benign hyperplasia, prostatitis	Suprapubic prostatectomy	Immediately before Immediately after 8 days after	0 35 1 7 0 36		General (sodium pent and nitrous oxide)	Yes
9	A P	66	Carcinoma	Suprapubic prostatectomy	6 days before Immediately before Immediately after 3 days after	0 50 0 61 2 5 0 39		General (sodium pent)	Yes
10	C D	76	Benign hyperplasia	Suprapubic prostatectomy	12 days before Immediately before Immediately after 19 days after	0 46 0 38 2 1 0 33	1350	General (sodium pent and nitrous oxide)	Yes
11	H G	66	Benign hyperplasia	Suprapubic prostatectomy	4 days before Immediately before Immediately after	0 29 0 03 4 3		General (sodium pent and spinal)	Yes
12	M U	66	Benign hyperplasia	Suprapubic prostatectomy	3 days before Immediately before Immediately after	0 37 0 00 2 1		General (sodium pent and nitrous oxide)	Yes
13	S L	61	Benign hyperplasia prostatitis	Perineal enucleation prostatectomy	Immediately before Maximal trauma 1 hr after 24 hrs after	0 44 9 2 16 9 0 12		General (sodium pent and ether)	Yes
14	A S	63	Benign hyperplasia	Retropubic prostatectomy	Immediately before Maximal trauma 1 hr after 22 hrs after	0 80 1 4 1 5 0 70		General (sodium pent ether and nitrous oxide)	Yes
15	J S	81	Benign hyperplasia	Suprapubic prostatectomy	Immediately before Immediately after 4 hrs after 24 hrs after	0 16 8 2 9 1 0 2		General (sodium pent and nitrous oxide)	Yes

Case Number	Patient	Age	Prostatic Diagnosis	Nature of Surgery	Time Relative to Maximal Trauma	Serum Acid Phosphatase Units/100 cc.	Tissue Acid Phosphatase Units/gm.	Anesthesia	Significant Elevation
16	E. H.	50	Benign hyperplasia; prostatitis	Suprapubic prostatectomy	Immediately before Immediately after 3 hrs. after 21 hrs. after	0.12 0.12 0.72 0.18		General (sodium pent. and nitrous oxide)	No
17	S. J.	61	Benign hyperplasia	Suprapubic prostatectomy	2 days before Immediately before 90 min. after 18 hrs. after	0.61 1.1 23.1 0.48		General (sodium pent. and nitrous oxide)	Yes
18	V. M.	68	Carcinoma	Perineal biopsy of prostate	6 days before Immediately before Maximal trauma 2 hrs. after 4 hrs. after 22 hrs. after	0.91 0.88 2.4 2.9 1.5 0.61		General (sodium pent. and ether)	Yes
19	A. A.	52	Benign hyperplasia; prostatitis	Perineal biopsy of prostate; TUR of prostate	2 days before After passage of sound Maximal trauma 3 hrs. after 5 hrs. after 22 hrs. after	0.19 0.43 0.10 2.1 0.97 0.21		General (sodium pent. nitrous oxide and ether)	Yes
20	L. S.	63	Carcinoma	Perineal biopsy of prostate	Immediately before Maximal trauma 1 hr. after 3 hrs. after 18 hrs. after	0.42 0.0 0.28 0.32 0.32		General (cyclopropane)	No
21	F. D.	65	Benign hyperplasia; prostatitis	Retropubic prostatectomy	Immediately before Maximal trauma 90 min. after	0.58 1.3 1.2		General (sodium pent. and spinal)	Yes

22	A B	70	Benign hyperplasia, focal infarction, prostatitis	Retropubic prostatectomy	12 days before	0.74		Spinal	Yes
					90 min after	1.5			
					4 hrs after	0.67			
23	S N	70	Benign hyperplasia	Perineal biopsy of the prostate	Immediately before	0.30		Spinal	Yes
					Maximal trauma	0.32			
					Immediately after	3.9			
					1 hr after	0.74			
					21 hrs after	0.88			
24	H S	71	Benign hyperplasia	Retropubic prostatectomy	Immediately before	0.59		General (ether)	Yes
					Immediately after	2.0			
25	G C	72	Benign hyperplasia	Retropubic prostatectomy	Immediately before	0.27		General (sodium pent and nitrous oxide)	Yes
					Maximal trauma	0.51			
					Immediately after	0.94			
					1 hr after	0.71			
					2 hrs after	0.94			
					5 hrs after	0.30			
					8 hrs after	0.27			
					11 hrs after	0.21			
					14 hrs after	0.19			
					17 hrs after	0.20			
					20 hrs after	0.18			
26	H J	64	Benign hyperplasia, prostatitis	Suprapubic prostatectomy	Immediately before	0.19	1205	General (cyclopropane)	Yes
					Maximal trauma	3.7			
					Immediately after	4.0			
					1 hr after	3.6			
					2 hrs after	2.1			
					3 hrs after	1.7			
					6 hrs after	1.2			
					9 hrs after	0.67			
					12 hrs after	0.44			
					15 hrs after	0.23			
					18 hrs after	0.17			
					22 hrs after	0.37			

prostatic enlargement or prostatic carcinoma in whom some type of surgical procedure on prostatic tissue was contemplated.

The plan of the experiment was to obtain blood specimens for serum acid phosphatase determinations on each patient at the following times:

1) Preoperatively, at various times prior to surgical manipulation of the prostate. Specimens designated "immediately before" were obtained after the patient had been anesthetized but before the actual operative procedure had begun.

2) Operatively, during that portion of the surgical procedure when prostatic trauma was estimated to be maximal. Such times were designated "maximal trauma" and include specimens obtained during the course of prostatic enucleation through either the suprapubic, retropubic or perineal route.

3) Postoperatively, at varying time intervals after conclusion of the operative procedure. Specimens designated "immediately after" were obtained at the conclusion of the operative procedure, usually within 30 minutes of the time of "maximal trauma."

The number of serial determinations of serum acid phosphatase carried out on the patients varied. To avoid any pretense at selection, however, all cases studied have been included in the tabulation of data, provided only that at least one preoperative or one postoperative acid phosphatase assay was available in addition to the determination made at the time of "maximal trauma" or "immediately after."

RESULTS

The data are presented in table 1. In 20 of 26 cases a significant elevation (or further elevation) in serum acid phosphatase occurred in association with the surgical trauma. In one of the 26 cases the surgical trauma was directed at a metastatic inguinal lymph node and if this case is eliminated, there were 20 elevations in 25 instances of direct surgical trauma to the prostate. Of these 25 cases, 20 had benign prostatic disease with 17 exhibiting elevations and 6 had prostatic cancer with 3 exhibiting elevations.

In 11 instances 2 or more observations of the serum acid phosphatase level were made within the 24-hour period subsequent to "maximal trauma." In 9 of

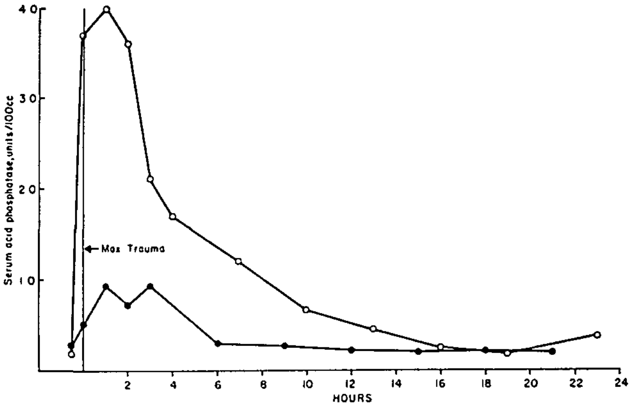

Fig. 1

these cases significant elevations in serum acid phosphatase occurred. It is of note that 5 of these 9 patients showed levels of serum acid phosphatase 1 to 4 hours postoperatively which were as high or higher than those found at the time of "maximal trauma" or "immediately after."

In only 2 cases (Nos. 2 and 3) was the serum acid phosphatase elevated prior to trauma and in neither of these cases did further elevation result from the trauma. With the exception of case 3, in which the diagnosis of prostatic carcinoma was made on clinical evidence only, each patient had histologic proof of the cited diagnosis. In 3 patients the acid phosphatase content of the surgically excised tissue was determined. In one patient (case 5) separate tissue acid phosphatase assays from different areas in the same prostate are recorded. The type of anesthesia and the anesthetic agents employed in each case are indicated.

In figure 1 the serum acid phosphatase levels of 2 patients (cases 25 and 26) submitted to retropubic and suprapubic prostatectomies, respectively, for benign prostatic hyperplasia, are plotted against time. Case 25 received 1000 cc of whole blood, 500 cc of 5 per cent glucose in distilled water and 500 cc of normal saline during the operative procedure which was difficult and required 3 hours for its completion. Case 26 received no transfusion but received an infusion of 1000 cc of 5 per cent glucose in distilled water which was completed within an hour of the completion of operation. In case 26 serial determinations of serum protein carried out in parallel with the serum acid phosphatase assays did not suggest any dilution. In case 25 the peak serum acid phosphatase value, 0.94 units, did not exceed the limits of the normal range but in view of the preoperative and later postoperative values, this was considered a significant elevation.

DISCUSSION

The data reported extend previous observations regarding the induction of elevations of serum acid phosphatase as a result of prostatic massage to include elevations resulting from surgical trauma to the prostate. That the elevation in serum acid phosphatase following prostatic trauma is the result of a "leak" of prostatic acid phosphatase into the circulation is a reasonable assumption although the data presented do not establish this point. A somewhat analogous situation is the rise in serum amylase and/or serum lipase activity which may result in normal subjects when pancreatic secretion is stimulated in the face of a contracted sphincter of Oddi.[8]

Although the data are insufficient to justify precise estimates of relative incidence, it is evident that trauma either to the benign or cancerous prostate may result in elevations of serum acid phosphatase. Elevations in association with surgical trauma occurred in 20 of 26 cases; 3 of 6 with prostatic carcinoma and 17 of 20 with benign prostatic disease. Further elevation in serum acid phosphatase following surgical trauma did not occur in the two instances of prostatic cancer in which elevations were present preoperatively. Needle aspiration biopsy of the prostate was carried out in one (No. 3) of these 2 cases and inguinal lymph node biopsy in the other (No. 2). Although there was considerable local trauma in conjunction with the latter procedure, the acid phosphatase content of the tissue was only 24 units per gram of tissue. In the latter case (No. 2) also, small rises in serum acid phosphatase could well have been missed in the face of the initially high levels. Indeed, in case 2, a rise from 68.4 units to 72.8 units in serum acid phosphatase did occur but we were loath to attribute significance to this relatively small change.

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It is of interest that some of the data indicate a continuing rise of serum acid phosphatase for several hours after the conclusion of the operative procedure. Since the serum acid phosphatase level is the resultant of production, release, inhibition, and removal of the enzyme, it is impossible from the data to determine which of these factors is primarily responsible for this continued rise. In the face of known operative trauma with gross disruption of tissues, a continued "leak" of enzyme into the circulation seems a likely explanation for such increases in serum acid phosphatase, however. This explanation seems especially applicable since in no case in this series was a total prostatectomy, removing the source of prostatic acid phosphatase, performed. In those patients in whom observations of serum acid phosphatase were made 18 to 24 hours following prostatic trauma, the serum acid phosphatase had, with one exception (case 23), returned to the preoperative level.

Since elevations of serum acid phosphatase were known to persist 3 to 4 hours following trauma in some cases, it was of interest to determine more exactly how long such elevations might persist. Accordingly, in 2 cases (Nos. 25 and 26) determinations of serum acid phosphatase were made hourly for the first 3 hours after "maximal trauma," and every 3 hours for the succeeding 18 hours. The results are shown in graphic detail in figure 1. In case 25 the elevation in serum acid phosphatase was so small that it was difficult to assess the time at which it returned to the preoperative level. However, it appeared to be at about 12 hours. The picture was complicated by operative hemorrhage, which necessitated the transfusion of 1000 cc of whole blood, the acid phosphatase of which was presumably at the normal low level. In case 26 there was a marked rise in serum acid phosphatase, which reached a maximum of 4.0 units one hour after "maximal trauma," and declined to the preoperative level in 16 hours. In both case 25 and case 26 the possibility of changes in serum acid phosphatase levels as a result of unrecognized fluid shifts between intracellular and extracellular compartments cannot be ruled out.

It has been known for some time that prostatic acid phosphatase is unstable at the pH and temperature of the bloodstream, and the conditions of inactivation have been studied by one of us.[9] Such inactivation is probably the principal mechanism involved in the disappearance of the enzyme from the plasma *in vivo*. London and coworkers[10] have postulated a half life of 5 hours for the enzyme at normal body temperatures. The curves shown in figure 1 do not provide a valid basis for an estimation of half life because, as suggested above, the enzyme probably continues to "leak" from the surface of the remaining prostatic tissue after removal of the obstructing portion of the gland There is no good way of estimating the extent and duration of this process, although the continued rise of the serum acid phosphatase for one or more hours after the conclusion of the operation suggests that it may be considerable and the attainment of normal values of serum acid phosphatase after 16 to 24 hours makes it probable that such "leakage" has ceased by this time Inspection of the curves, however, shows that the half life is certainly not greater than 5 hours, and possibly less Study of patients submitted to total prostatectomy, in whom leakage of enzyme from residual prostatic tissue would not complicate the picture, should clarify the latter question

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The production of elevations in the serum acid phosphatase as a result of prostatic trauma raises several questions The first concerns the degree of trauma necessary to produce an elevation of serum acid phosphatase That prostatic massage and prostatic surgery will produce such elevations is beyond question, but the effects of such "physiologic" trauma as sexual function and bowel function remain undefined The possible clinical significance of observations on such points rests on the fact that improvements in methods for the detection of elevations in serum acid phosphatase are being proposed as means for the earlier recognition of prostatic carcinoma If such measures prove successful, it becomes of obvious importance to fully define conditions or circumstances other than prostatic carcinoma which are capable of producing such elevations in serum acid phosphatase

A second question concerns the possibility that prostatic enzymes other than acid phosphatase may also enter the circulation Huggins and Neal[11] and Huggins and Vail[12] studied proteolytic enzymes in the semen and prostatic fluid of man Tagnon et al [13] have described a hemorrhagic diathesis, in certain patients with extensive prostatic cancer, attributed to the release of such proteolytic enzymes into the circulation It is conceivable that proteolytic enzymes may enter the circulation in a manner analogous to prostatic acid phosphatase and that such enzymes may have some role both locally and systemically in the occurrence of hemorrhage following prostatectomy

CONCLUSIONS

Elevations in serum acid phosphatase may occur following surgical trauma of the benign or cancerous prostate

Serum acid phosphatase levels may increase for several hours following the inciting trauma, at least if residual prostatic tissue is present

Serum acid phosphatase values, elevated by operative trauma to the prostate, return to their preoperative level within 24 hours of operation In 2 cases studied in detail, the preoperative level was reached in 12 to 16 hours

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AN ADJUNCT IN THE MANAGEMENT OF THE PENOSCROTAL ABSCESS

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A pathological lesion at the penoscrotal junction of the urethra is a frequent complication of paraplegia.[1, 2] This condition has been described as a "decubitus ulcer-like" lesion of the urethra;[1] its pathogenesis consists essentially of an irritation of the mucosa by the intraurethral catheter leading to a periurethral abscess at the penoscrotal angle. The diagnosis is made clinically either by palpation of a penoscrotal induration or by the presence of urethral (purulent) discharge around the catheter. The urethrogram verifies the diagnosis.[3]

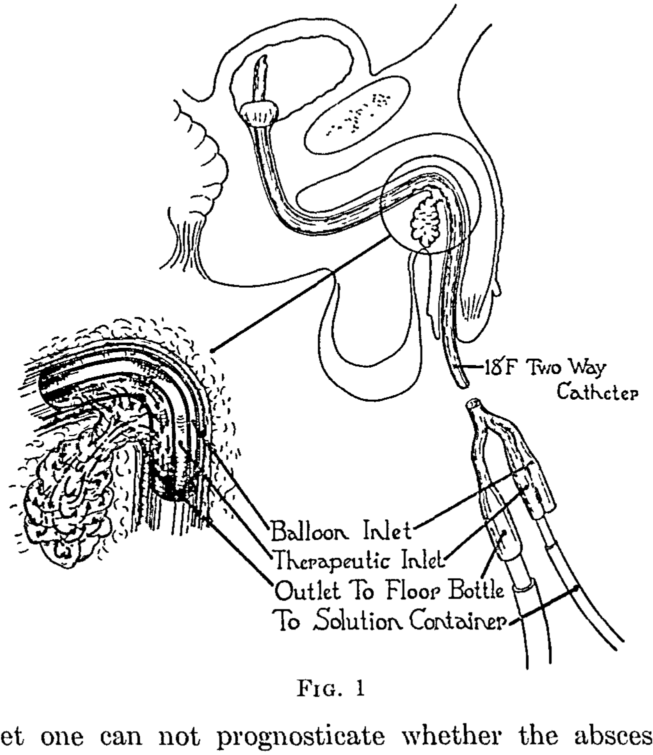

FIG. 1

At the onset one can not prognosticate whether the abscess will resolve, leaving a urethral diverticulum, or will perforate through the skin and form a fistula. While diverticula are operated on only if they are of large size, surgery is absolutely indicated for penoscrotal fistulas. Every attempt is, therefore, justified at preventing the formation of a fistula from an abscess.

Accepted for publication May 31, 1955.

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A practical preventive method is shown in the attached diagram, its purpose is to remove the purulent discharge of the abscess by irrigation in order to halt necrosis and possible perforation of the skin This can be done by an ordinary 18F Foley bag two-way catheter in which multiple holes are drilled prior to sterilization of the catheter into the outlet channel These holes extend about 1 inch proximal and distal to the meatus of the fistula The prescribed solution is introduced from a bottle suspended to a standard as a continuous slow drip day and night The solution enters the bladder whence it returns via the outlet channel, bathes the urethra and the abscess by way of the perforations in the outlet channel and eventually drains through the distal perforations back again into the outlet channel

In addition to this irrigation, evacuation of the purulent contents is encouraged by gentle pressure every 2 hours

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PREVENTION AND TREATMENT OF THROMBOPHLEBITIS AND PULMONARY EMBOLISM IN GENITOURINARY SURGERY

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It is generally conceded that thrombophlebitis, phlebothrombosis and pulmonary embolism occur more frequently after surgical intervention in the pelvis, particularly on the organs of the genitourinary tract, than elsewhere in the body. The incidence is highest among debilitated and aged patients, many of whom have coexisting cardiovascular or lung disease, among women (Towbin) and among patients with inflammatory processes in the lower extremities. Since the older age group is enlarging, life expectancy now having reached 67 years in the United States, older patients are undergoing operations.

The expected frequency of occurrence of pulmonary embolism complicating all surgical procedures has been recorded as 0.174 per cent (Ochsner et al.), 0.1 to 0.2 per cent (de Takats and Jesser) and 0.6 per cent (Carlotti et al.). Zimmerman, Miller and Marshall noted fatal embolism in 1 in 2,000 operations. Thrombophlebitis or phlebothrombosis in the lower extremity is encountered in about 60 per cent of those presenting pulmonary embolism (Belt). Ceelen pointed out that careful dissection of the arterial tree of the lung would probably reveal emboli in 75 per cent of the cases of thrombosis in other parts of the body. Clinically many cases of pulmonary embolism are undoubtedly overlooked, being mistaken for diseases such as coronary occlusion, bronchial pneumonia, pleuritis with effusion, or atelectasis.

The incidence of pulmonary embolism is indeed higher following prostatic surgery than operations on other organs of the genitourinary tract. In a series of 477 patients who underwent prostatic operation from 1929 through 1948 (Mathé), pulmonary embolism complicated 2 (1.6 per cent) of 123 prostatectomies; phlebothrombosis, 4 (0.88 per cent) of 354 transurethral prostatic resections. Most of these preceded the routine use of antibiotic therapy.

Immediately after operation there is a decrease in metabolic activities, decrease in blood flow and pressure, as Virchow pointed out in 1846, and changes in the cellular constituents of the blood. Viscosity of the blood is increased owing to a rise in the concentration of fibrinogen and albumin globulin. The complex clotting mechanism is also altered. Precipitating factors include postoperative leukocytosis. The number of platelets liberating thrombokinase rises and this hastens coagulation of stagnating blood. All of these mechanical and chemical factors favor the actual formation of thrombi.

Inactivity also promotes stagnation of blood and consequently formation of clots. In 1935 Frimann-Dahl determined the emptying time of the saphenous vein in patients bedridden for a long time after operation. He injected contrast

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medium into the saphenous vein and observed its course under fluoroscopy In normal patients it disappeared in 5 to 30 seconds, in bedridden patients in from 1 to 2 minutes

Between 1929 and 1948 we encountered fewer cases of fatal pulmonary embolism after kidney operations following which the foot of the bed was routinely elevated in order to maintain the kidney in place As further evidence of the efficacy of this simple measure in promoting venous circulation, in the practice of one of us (Salomon) only 1 case of pulmonary embolism followed 1,500 high ligations and radical resections of the saphenous vein in which the Trendelenburg *position was used immediately postoperatively, and in this single case the embolism* was minor

These observations led us to elevate the foot of the bed immediately after intervention on the prostate and other organs of the genitourinary tract and in vein surgery The particular advantage is that the foot of the bed can be elevated before the patient is ambulatory Since phlebothrombosis and thrombophlebitis usually affect the tributaries of the vena cava, especially the femoral, calf or pelvic veins, the underlying principle of the measure becomes apparent This measure, in addition to passive and active exercise, early ambulation and other supportive measures, best assures increased venous return flow and thereby minimizes the formation and propagation of clots Blood that flows fairly rapidly is less likely to clot than stagnant blood

This measure has also been advocated by others In 1934 Gray reported on 276 cases in which the foot of the bed was elevated 11 inches for 24 hours following operation The incidence of pulmonary embolism was 30 per cent lower in this group than in another group of 3,153 patients in which this position was not used In 1940 de Takats and Jesser advocated use of this position along with other measures to prevent pulmonary embolism It has been repeatedly pointed out that prolonged bed rest of middle and older aged patients favors the occurrence of thrombophlebitis—in as high as 52 7 per cent (Hunter et al)

Early ambulation has been almost universally adopted after operation, including vein surgery Prior to the widespread advocation of early ambulation, when the patient who had undergone a vein operation was kept in bed for from 10 to 14 days, the incidence of pulmonary embolism was so high that this type of surgery almost fell into disrepute

PROPHYLACTIC TREATMENT

Following prostatectomy and many other extensive operations on the genitourinary tract, because of the effects of the anesthesia, the stress of the operation, the danger of hemorrhage and the debilitated condition of many of the patients, they are unable to be out of bed in less than 3 to 5 days Therefore, to promote venous circulation, immediately after the patient returns to his room the foot of his bed is elevated, about 12 inches It is important to avoid placing the patient in the jackknife position, for this impedes, rather than promotes, venous return flow Tight abdominal binders are not used for the same reason

One of course cannot hope that this measure will succeed in preventing pulmonary embolism in every case. One must realize that it is one of the most common causes of medical death in the aged. Another possibility has been pointed out: In exceptional cases even small emboli obstructing only a small portion of the lung may provoke autonomic reflex spasm of the entire pulmonary tree, and this may cause death.

Of interest is a case of pulmonary embolism following intubated ureterotomy for hydronephrosis. Early ambulation was impossible, and the patient was necessarily kept in the Trendelenburg position for 17 days after operation. When the nephrostomy tube was removed and she was able to be out of bed, nonfatal pulmonary embolism developed in the left lung base.

Before the patient is ambulatory, passive and active exercise are employed to stimulate circulation. He is encouraged to become ambulatory as soon as possible if no complications occur. Routine antibiotic therapy controls infection and minimizes the occurrence of the infectious type of thrombophlebitis.

ROENTGENOLOGIC DIAGNOSIS* OF PULMONARY EMBOLISM

Pulmonary embolism is so often mistaken for bronchial pneumonia, pleuritis with effusion and atelectasis that it is well to discuss the differential diagnosis. Sudden onset of pain in the chest, cough, hemoptysis and febrile reaction occurring within 2 weeks of operation should lead the physician to suspect pulmonary embolism and to repeat roentgenologic studies every 2 or 3 days.

In phlebothrombosis the aseptic clot is more likely to occlude a larger vessel, producing diffuse, noncircumscribed and nonspherical density which usually involves a lobule of the lung. As its shape becomes demarcated it takes on the appearance of a pyramid, with the apex pointing to the hilus. The x-ray appearance resembles that in pneumonitis. The shadow usually disappears within 3 to 5 days.

In thrombophlebitis its infectious nature is revealed by clinical studies. The area of increased density usually occurs in the periphery of the lung, often at its base, and tends to spread out, as shown by serial x-ray studies. The infarct resulting from the embolus soon gives rise to pleural effusion, and one observes an uncircumscribed shadow which fades out into well-aerated lung tissue. A cavity is likely to develop at the site of infarction.

Roentgenologic distinctions between the above types of pulmonary embolism and bronchial pneumonia, pleuritis and atelectasis are not clean cut. In bronchial pneumonia more than one lung lobe is likely to be involved, but this may also be true of the larger saddle emboli. Pleuritis with effusion cannot be distinguished from embolus by x-ray. Atelectasis can be readily differentiated because the lung becomes airless in 6 to 8 hours due to obstructing secretions or vomitus in the bronchus. One soon observes compensating shift of the opposite lung toward the atelectatic side. If the embolic process ends in fibrosis one must differentiate it from a fibrotic tuberculous lesion, but this usually becomes calcified. Residual fibrosis without calcification usually indicates a healed infarct. Small infarcts resulting from multiple emboli, so often present, usually cast no shadow and must be detected by clinical studies; these small lesions are relatively unimportant.

*Dr. Charles S. Capp was the roentgenologic consultant in the cases to be described.

TREATMENT

Thrombophlebitis and phlebothrombosis The treatment of these two conditions is quite similar In phlebothrombosis the uninfected clot grows rapidly, is friable and a segment is more likely to become dislodged and form an embolus which passes on into the lung Theoretically in thrombophlebitis, because of the infectious process, there is greater tendency to fixation of the clot

The foot of the patient's bed is elevated immediately and remains so until the pulse rate and temperature drop—usually in 5 to 10 days

We use the Bauer method of heparinization Heparin is given in a single dose of 100 to 150 mg intravenously 3 times a day until the pain, fever and pulse rate subside—usually in 10 to 14 days This is continued in gradually diminishing doses, depending on the clotting time, for about a week or 10 days after the patient becomes ambulatory It is important to check the coagulation time the first day the drug is given and thereafter every 1 to 2 days If it exceeds 20 seconds the dose of heparin should be reduced to half and then enlarged as the coagulation time decreases

Many clinicians begin by using both heparin and dicumarol, and when the prothrombin time has reached 20 to 30 seconds use of heparin is discontinued In our experience use of dicumarol has been more often followed by hemorrhage If it should occur one should administer vitamin K and whole blood This inconvenience is reduced by the use of heparin alone

Recently trypsin in the form of parenzyme (0 5 cc intramuscularly 3 or 4 times a day) has been advocated because of its lytic effect on the thrombus It can be used in conjunction with heparin and the antibiotics Innerfield observed the lytic effect of trypsin on grossly visible thrombi in 18 patients with chronic recurrent thrombophlebitis In all 18 patients the blood clots disappeared without becoming pulmonary emboli Prior to this, 7 of these patients had had one episode, and three had had several episodes of embolism

Antibiotic therapy is instituted as soon as the diagnosis is made and is continued throughout the acute stage The affected lower extremity is bandaged from the ankle to the thigh, snugly, but not too tight Bandaging relieves pain and prevents edema Heat or ice bags are employed for severe pain Passive and active exercise are instituted as soon as the febrile reaction subsides

We prefer not to ligate the femoral vein, because of the difficulty in locating the exact site of the phlebothrombosis In addition, the clot may be situated in the venous system even above the ileofemoral junction, in which case it would be necessary to ligate the vena cava itself Femoral vein ligation augments and prolongs postphlebitic extensive edema of the leg

Paravertebral block and lumbar sympathectomy have been used by Leriche and Kunlin and many others for the relief of postoperative phlebitis, arterial spasm, pain and edema and for prevention of embolism We do not recommend this major surgical procedure, because good results can be achieved by more conservative means

The recommended treatment for acute thrombophlebitis and phlebothrombosis, then, is elevation of the foot of the bed, heparinization, application of heat or cold, bandaging of the affected limb and antibiotic therapy, and later, passive and active exercise, as soon as possible.

Treatment of the postphlebitic syndrome is beyond the scope of this paper.

Pulmonary embolism. About 60 per cent of the patients with massive pulmonary embolism succumb within 15 minutes of its occurrence (Nygaard). Treatment of the remaining 40 per cent includes anticoagulant and antibiotic therapy. Oxygen is of course given. Papaverine (30 mg.) and atropine (0.4 mg.) are both given immediately, intravenously, to combat retrosternal pain.

Embolectomy, suggested by Trendelenburg in 1908, carries a reported mortality rate of approximately 93 per cent (Nygaard), a rate appreciably exceeding that in our series in which no operation was carried out. Although this operation might be undertaken under optimal conditions it is not recommended for general use.

In patients with repeated pulmonary embolism, the femoral vein should be ligated high to prevent recurrence.

ANALYSIS OF CASES

In the years 1952, 1953 and 1954, at Saint Mary's Hospital in San Francisco, 18 cases of pulmonary embolism complicated 9,005 major operations—an incidence of 0.19 per cent. Five were fatal—1 in 1,801 cases (0.055 per cent) and 13 were not (table 1). Most of the emboli were accompanied by pleuritic pain,

TABLE 1. *Postoperative pulmonary embolism*

Operation	Cases, Number	Time after Operation
Nonfatal embolism		
		days
Repair of fractured femur	2	12 30
Ligation of femoral or saphenous vein	2	7 12
Transurethral prostatic resection	2	13 26
Intubated ureterotomy	2	17 30
Delivery	2	5 9
Gastric resection	1	6
Removal of bunion	1	11
Repair of fracture of the leg	1	11
Fatal embolism		
Cholecystectomy	2	9 36
Removal of ovarian cyst	1	5
Transurethral prostatic resection.	1	8
Nephropexy	1	24

hemoptysis and febrile reaction. The roentgenograms revealed characteristic diffuse, noncircumscribed increased density of the lung area at the site of the embolus, so often mistaken for pneumonitis or pleuritis with effusion.

Except in our group of 337 urologic surgical patients and the 1,500 patients who underwent vein surgery, the foot of the bed was not routinely elevated immediately after operation. Passive exercise and early ambulation were also instituted in our cases as soon as possible—usually 2 or 3 days after operation.

During this same period, in a total of 382 operations on veins of the leg there were 2 cases (0.52 per cent) of nonfatal pulmonary embolism.

Of the 9,005 operations, 1,001 were on the genitourinary tract. Four cases (0.60 per cent) of pulmonary embolism occurred in 664 patients who were not placed in the Trendelenburg position immediately after operation, two (0.3 per cent) were fatal. Two cases of nonfatal pulmonary embolism occurred in 337 (0.59 per cent) in which the foot of the bed was elevated. There were no fatal cases in this group.

Once we were cognizant of the value of this procedure, every patient was particularly scrutinized postoperatively for signs and symptoms of pulmonary embolism. Roentgenologic examination was carried out repeatedly in each suspected case, and x-ray evidence of embolism was meticulously sought. Special pains were taken to detect even slight embolism. In 2 of the 4 nonfatal cases that did occur the clinical diagnosis would otherwise have been lung disease.

Two pulmonary emboli (1 fatal), an incidence of 1.03 per cent, followed 193 prostatic interventions in which the foot of the bed was not elevated, and 1 nonfatal embolus (0.71 per cent) occurred in 134 in which it was.

The incidence of pulmonary embolism was only slightly different in the two groups (table 2), but the fatality rates differ. Two of the 4 cases in which the prophylactic measure was not taken were fatal, and no fatalities occurred in the group in which it was taken. It seems likely that the difference may be explained by the fact that in the latter group the venous circulation was more rapid. Elevation of the foot of the bed increases return flow through the venous system and lessens the likelihood of propagation of the clot, minimizing formation of an embolus. As the thrombus forms the head is firmly attached to the intima of the vein, and as it develops the body and tail float free within the vein. It seems logi

TABLE 2. *Effect of use of the Trendelenburg position on the incidence and mortality of pulmonary embolism*

Operation		Trendelenburg Position	Embolism		Mortality	
Type	Number		Cases	Per cent	Number	Per cent
Genitourinary	337	Used	2	0.59	0	0
	664	Not used	4	0.60	2	0.3
Prostatic	134	Used	1	0.71	0	0
	193	Not used	2	1.3	1	0.5
Vein	1,500	Used	1	0.06	0	0
	382	Not used	2	0.52		
All types	9,005		18	0.19	5	0.05

cal to assume that increased venous return flow resulting from elevation of the foot of the bed interferes with further development and propagation of the clot, minimizing the detachment of a larger fatal embolus.

SUMMARY

The prophylactic measures we recommend for the prevention of pulmonary embolism consist of elevation of the foot of the bed, passive and active exercise immediately after operation, to assure increased venous return flow, and early ambulation to maintain that flow, antibiotic therapy and early treatment of thrombophlebitis and phlebothrombosis. They assure increased venous flow during the 1 and 5 days after operation when, because of the effects of the anesthesia, stress of the operation, danger of hemorrhage and general debility, the patient is unable to get out of bed. They eliminate blood pooling, lessen the likelihood of the development and propagation of the clot and minimize the detachment of the larger fatal embolus.

All patients with suspicious clinical evidence of pulmonary embolism were meticulously scrutinized for roentgenologic evidence of emboli. Special care was taken to differentiate these from bronchial pneumonia, pleuritis with effusion and atelectasis.

Eighteen cases of pulmonary embolism, 5 fatal and 13 nonfatal, complicated 9,005 major operations at Saint Mary's Hospital in the years 1952, 1953 and 1954, an incidence of 0.19 per cent. Six cases (0.59 per cent) of pulmonary embolism complicated 1,001 operations on the genitourinary tract. The preventive measures described were used in 337 cases, and in these there were 2 cases of *nonfatal* pulmonary embolism. Four cases, 2 (0.60 per cent) fatal, occurred in 664 cases in which they were not all carried out.

In the older group of patients, 2 pulmonary emboli (1.3 per cent), 1 fatal, followed 193 prostatic interventions in which the Trendelenburg position was not used immediately after operation; 1 *nonfatal* embolism (0.71 per cent), in 134 cases in which it was used.

In a total of 382 operations on veins of the leg, 2 cases (0.52 per cent) of nonfatal pulmonary embolism occurred, and in these two the foot of the bed was not elevated immediately after operation. In 1,500 similar operations in which it was, only 1 case of embolism occurred and it was minor.

Pulmonary embolism is one of the most frequent causes of medical deaths in the aged, so we cannot hope that the prophylaxis recommended will prevent its occurrence in every case. However, it is one step in minimizing its occurrence. We make a plea for the more general use of these simple preventive measures based on sound principle.

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A STUDY OF HUMAN URINE WITH THE ELECTRON MICROSCOPE

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The function of the kidney is to maintain the fluid, electrolyte, and acid-base balance of the organism while removing certain end products of protein metabolism from the blood plasma. It is generally believed that urine is formed in the mammalian kidney by the ultrafiltration across the endothelial membranes of the glomerulus of a fluid carrying all of the constituents of the blood plasma except the colloids.[1, 2, 3]

The formation of the urine is completed by certain functions of the tubular epithelial cells. These functions are: reabsorption, excretion, and the production of new substances which may pass either into the tubule fluid or into the blood plasma.

The physiological fluid (urine) thus formed is a solution usually described as water saturated or supersaturated with solutes. The solutes are the electrolytes, the nonelectrolytes (molecular substances in true solution), and the colloids. The term colloid does not apply to a chemical class of material but rather to a state of subdivision.[4] Thomas Graham, in 1861, classified all substances into two groups, crystalloids and colloids. However, it is now recognized that matter cannot be rigidly classified in this manner since many typical colloids, such as certain proteins, are crystallizable while practically all crystalloids may, under proper conditions, be brought into the colloidal state.[5]

If the particles of a substance are reduced in size until they become submicroscopic (0.001 micron to 1 micron) and are distributed throughout a second liquid substance, a colloidal solution is formed. The ability of the dispersed particles to remain in the colloidal state is influenced by the concentration of ions in the solution. In the absence of ions a lyophobic colloid is not stable and the colloid may settle out. In the presence of a large excess of electrolyte the colloid particles may be coagulated by ions of opposite charge. Electrophoretic studies of urine by Dr. E. A. Hauser[6] (reported by Butt) showed that the colloids of urine carry a net negative charge. Butt reasoned that these urinary colloids were beneficial because they adsorbed ions and thus increased the solubility of the crystalloids.

It is possible to separate the colloids from the crystalloids of the urine by dialysis. Boyce et al.[7] have isolated several urinary biocolloids, a salt-soluble protein component (fraction I), a soluble mucoprotein dialyzed at pH 4.5 (frac-

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tion II), and an insoluble polymerized form of fraction II. The lyophilized dry weight of the total urinary colloids for average adults is 0.0902 gm. per 24 hours. The amount of colloidal material in the urine has been determined by means of electrophoresis,[6, 7] surface tension,[8-10] and ultra microscope observations.[6, 10]

The electron microscope is another tool that can be used to study the crystalloids and colloids of urine. This paper describes techniques for the study of urines with the electron microscope. The urinary constituents visualized by means of these techniques are described.

METHOD

These electron microscope studies were initiated to gain a better understanding of the colloid-crystalloid relationships in urine. The electron microscope is ideally suited for the study of urinary colloids since its useful magnification reveals particles with diameters of one millimicron and larger. The microscope used in these studies was an RCA EMU.

The effective use of the electron microscope for the study of urine is entirely dependent upon the specimen preparation techniques used. These techniques should: 1) provide representative samples for fields of view; 2) furnish information on size, shape, and number of particles per field; 3) avoid the production of artefacts; 4) distinguish between the water-soluble dialyzable materials and materials not dialyzable through a collodion membrane against distilled water.

Uniformity of sampling is insured first by a vigorous mechanical shaking of the urine for one hour before the sample is taken. Representative samples are then obtained by atomizing small amounts of this urine on electron microscope specimen screens covered with thin collodion films. Each microdroplet in the atomized pattern should be a representative sample of the whole specimen.

A specially constructed glass atomizer powered with a filtered air supply at 40 pounds pressure was used to atomize approximately 1 lambda (1 one-thousandth of a ml.) of urine on the collodion films. The distance between the atomizing orifice and the collecting film was varied from 1 to 25 cm. At distances greater than 4 cm. the microdroplet patterns were round and discrete (fig. 1, *A*). This is an electron micrograph of an evaporated microdroplet of whole urine shadowed with uranium metal. If the microdroplets are collected at a distance of 1 cm. from the orifice, the droplets are scattered into irregular patterns (fig. 1, *B*). The intense force of the air blast causes the droplets to be blown into very thin layers before drying. The operation of the atomizer was finally standardized using an air pressure of 40 pounds and a spraying distance of 8 cm.

All specimens studied were given a thin coating of uranium metal evaporated at a 20° angle. This treatment enhanced the contrast of the specimen and revealed the third dimension of the particles. One-eighth inch circles of specimen screen supporting the specimen-carrying films were punched out just prior to their observation in the microscope.

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[9] Ravich, R. A. and Ravich, Abraham: J. Urol., **72:** 1050, 1954.

[10] Ravich, R. A.: Science, **117:** 561, 1953.

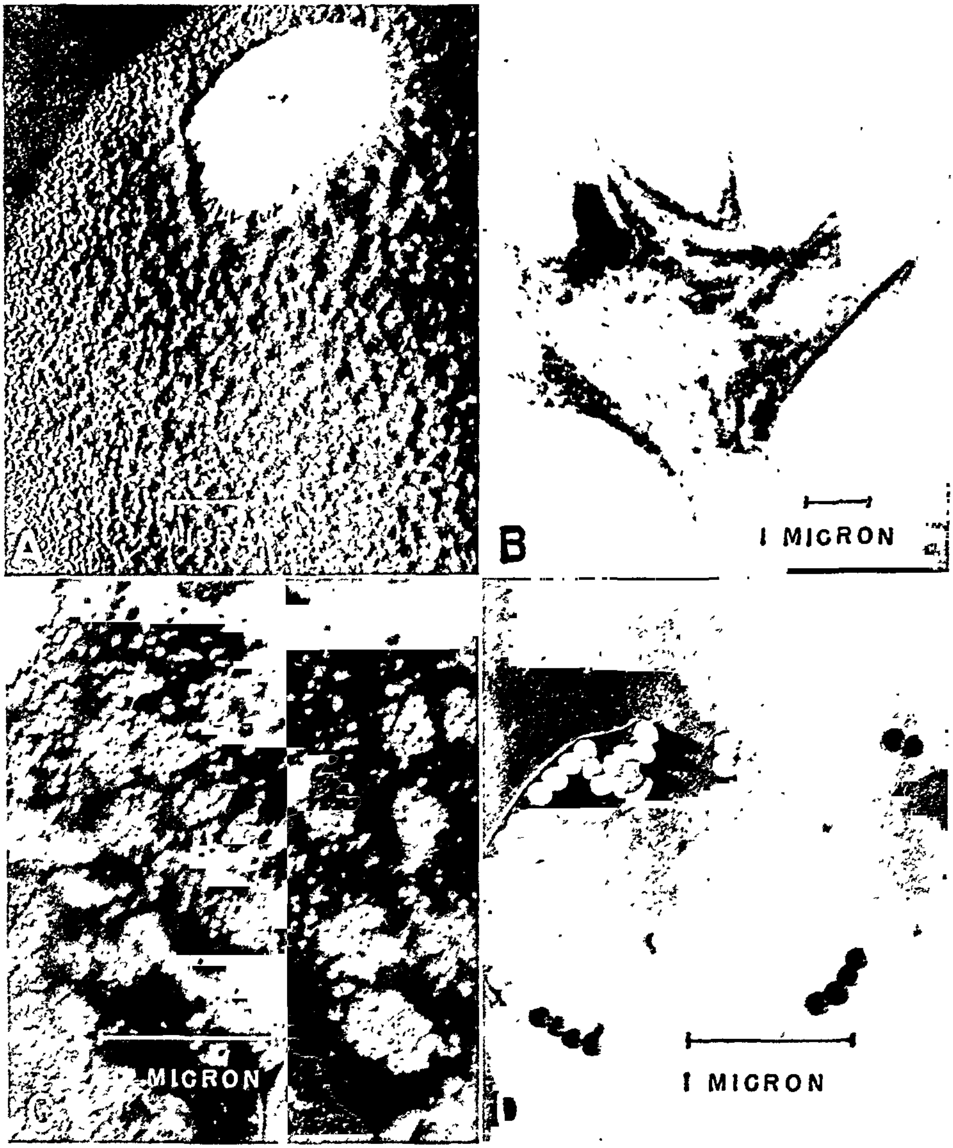

FIG. 1. Electron micrographs shadowed with uranium metal. *A*, portion of nondialyzed urine microdroplet collected at distance of 15 cm. from atomizing orifice containing one rather large microcrystal, numerous tiny microcrystals and many blotches of amorphous material. *B*, irregularly shaped microdroplet of nondialyzed urine collected 2 cm. from orifice of atomizer. *C*, internal portion of nondialyzed urine microdroplet containing numerous microcrystals overlaid with irregular blotches of amorphous material. *D*, polystyrene latex spheres (.132 microns in diameter) lying in circular pattern formed by evaporation of distilled water-polystyrene microdroplet.

The specimen-supporting films were used as dialyzing membranes in the following way. The films were placed under the atomizer and sprayed with an aliquot of urine. They were then floated on the surface of distilled water. The water diffused through the films and dissolved the salt residues which then diffused into the distilled water below. This technique was not satisfactory because the high salt concentration in the droplet residues caused relatively large amounts of water to come across the floating membrane, redistributing the colloids and moving them out of their original microdroplet patterns

The following technique was devised to give extremely slow initial rates of dialysis for the purpose of avoiding excessive redistribution of the colloids Blocks of 7 per cent agar covered with collodion film membranes were sprayed with urine microdroplets Dialysis was then allowed to proceed through the agar and the membranes to distilled water in petri dishes The 7 per cent agar competes with the salt residues for water across the collodion membranes Under these conditions the upper surfaces of the membranes are not flooded with water because a gradient of available water is established through the agar blocks Water is most available at the surface of the agar next to the distilled water and it is least available at the opposite surface (next to the dialyzing membrane) Thus only a small amount of salt will dissolve and diffuse through the membrane into the agar and through the agar into the water during the earliest stages of dialysis With the passage of time dialysis proceeds at increasing rates as water becomes more available This initial agar block dialysis is allowed to proceed for 48 hours at 70°F in petri dishes with covers slightly ajar Water lost from the dishes by evaporation is replenished several times daily to maintain a level extending ⅓ to ½ of the distance up the block

The following procedure was used in preparing the agar blocks Seven per cent agar was made up with one tenth of 1 per cent mercuric chloride to prevent growth of micro organisms during the dialysis process The agar was prepared by steam autoclaving for 15 minutes at 15 pounds pressure It was poured into petri dishes to a depth of 7 mm and allowed to cool When cooled the agar was transferred to the petri dish top using a spatula The dish top was then filled with distilled water and a collodion membrane was formed on the surface of the water by the spreading of a single drop of 1 per cent collodion in amyl acetate Water was then removed from the dish with a suction device allowing the membrane to settle on the agar surface The agar was removed from the dish top and placed on an adsorbent paper for 15 or 20 minutes while the membrane dried The agar covered with the membrane was then cut into blocks 2 by 2 cm and 7 mm thick These blocks were then ready to receive the atomized sample

After the initial dialysis of 48 hours through the agar blocks, the membranes were floated from the surfaces of the agar by gently lowering the blocks into distilled water These membranes were then allowed to float on water surfaces for an additional 24 hours to complete the dialysis It was assumed that all except the very insoluble salts had been removed by the initial dialyzing treatment through the agar

After the 24 hour dialysis on the surface of distilled water, the membranes were picked up on pieces of copper electro mesh specimen screens from below These membranes were allowed to dry for 30 minutes before placing in the metal evaporator

The location of the dialyzed spray droplet patterns in the electron microscope became more difficult because more than 99 per cent of the evaporated residue of the droplet had been removed It seemed desirable to add some easily recognizable colloid to the urine to aid in the location of the microdroplet patterns. A colloid which served this purpose very well was the polystyrene latex No. 15N-23 manufactured by the Dow Chemical Company. This latex occurs in the form of spheres having an average diameter of .132 microns with a standard deviation of 0.009. A suspension of these particles having a concentration of 2.4×10^{11} particles per ml. was made up. Equal volumes of the polystyrene latex suspension and urine were mixed and subjected to vigorous mechanical shaking for one hour. This mixture was then atomized on the membrane-covered blocks in the usual manner. Polystyrene latex used in this way enables the electron microscopist to locate the droplet patterns with ease and to estimate the extent of redistribution of the colloids occurring during dialysis. These latex particles are also of great value in the determination of the size of the urinary colloids. They are also used to determine the degree of magnification of electron microscope pictures. Comparative counts of colloids and polystyrene latex particles in microdroplet patterns will give a reliable estimation of the number of colloids per ml. of urine. Figure 1, *D* shows a circular pattern of a water suspension of the latex spheres sprayed on the collodion membrane.

All possible sources of colloid or colloid-like materials other than the urine or the standard polystyrene latex were checked periodically during the investigations. No particles other than the .132 micron spheres were found in the polystyrene preparations while the distilled water, compressed air, and the collodion used in forming the membranes appeared to be free of colloidal-like particles that might be confused with the particles occurring in the urine.

RESULTS

Urines, reported as normal by routine laboratory examination, obtained from 15 males and 15 females in the age group 20 to 30 years were studied. The samples were the first voided after breakfast. No other attempt was made to control any of the factors that might have been pertinent to the constituents of normal urine such as diet, water intake, exercise, stress, etc.

Thirty to 40 microdroplets were observed in the electron microscope before 5 were chosen and photographed as representative types for each specimen. Both dialyzed and nondialyzed preparations of each specimen were studied.

The studies on nondialyzed urines did show differences between specimens from different individuals. None of these observed differences could be correlated with the sex of the donor. The isolated microdroplets in any given specimen were usually quite similar in appearance.

The following components were found in the evaporated residues of microdroplets of nondialyzed urine.

A) Each microdroplet contained one or more irregularly shaped bodies one to two microns in diameter. These particles were very opaque to the electron beam (fig. 1, *A*). It was assumed that these particles were rather large microcrystals which existed as such in the urine because they were too large to have been grown in the extremely short evaporation time and because they disappeared completely during the dialyzing procedure.

B) Thousands of smaller particles having diameters in the 50–150 millimicron range were also seen in each microdroplet pattern. It was assumed that this material was composed of tiny microcrystals formed at the instant of drying from the dissolved urinary salts (fig. 1, *C*). These particles also disappeared with dialysis. Their size was somewhat dependent upon the rate of evaporation of the urine droplets. Since the atomizing techniques were standardized, it was assumed

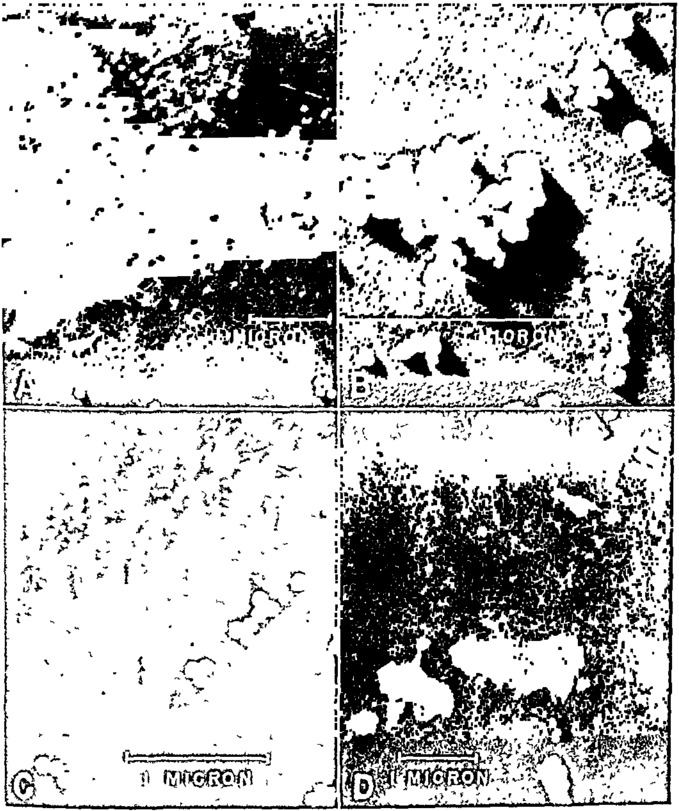

FIG. 2. Electron micrographs shadowed with uranium metal illustrating types of colloids found in normal dialyzed urine preparations *A*, portion of urine microdroplet containing thousands of type M spherical colloids (100 A U.), about 50 spherical type O colloids (600 to 1000 A.U.), six circular clumps of type F colloids, numerous crystal-like residues, and six polystyrene latex spheres. *B*, portion of urine microdroplet containing two polystyrene [illegible] umps of type P colloid *C*, portion of urine [illegible] latex spheres, about 25 type S spindle-shaped [illegible]s. *D*, portion of urine microdroplet containing crystalline material that was not removed by dialysis.

that the variations seen in the residues of microdroplets were not due to differences in drying times.

C) A third type of material was visible in most of the microdroplet patterns appearing as irregular blotches lacking uniformity in size and shape. This ma-

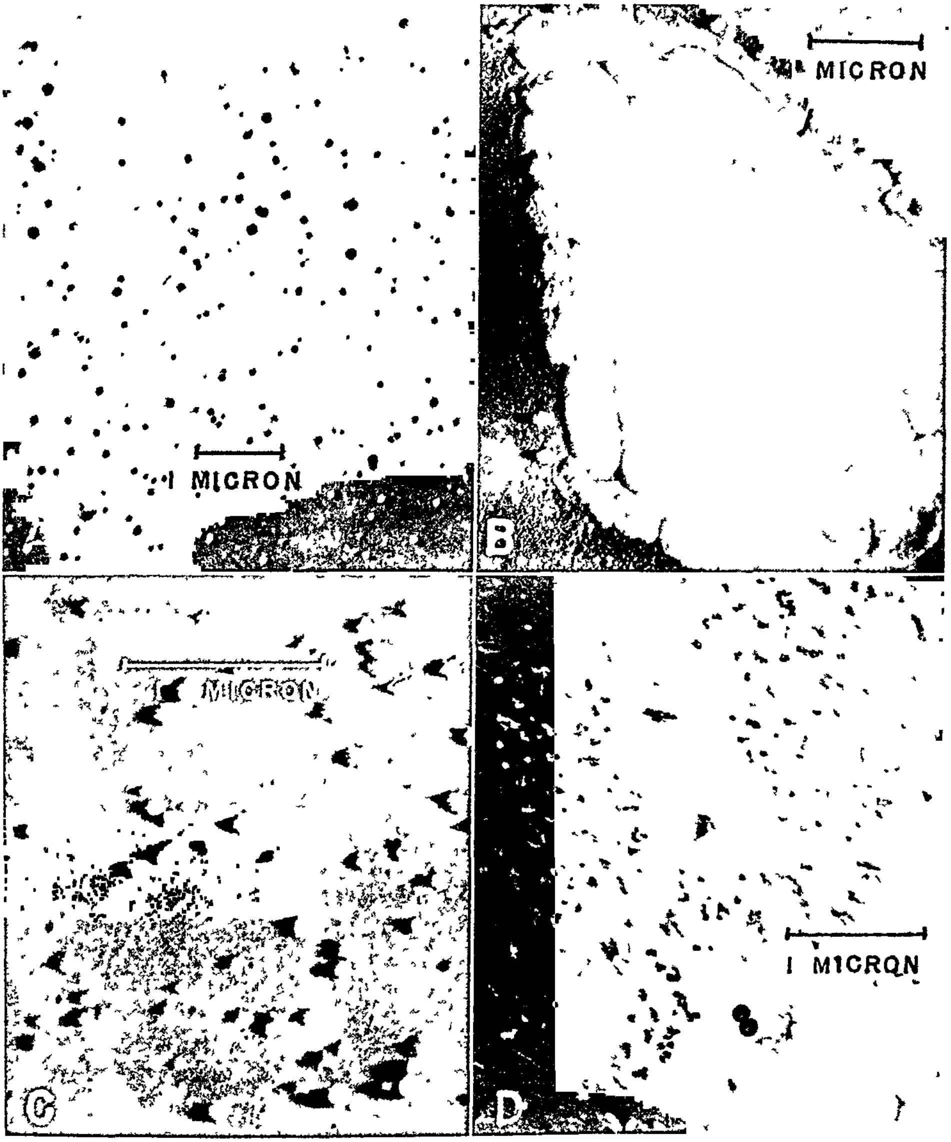

FIG. 3. Electron micrographs shadowed with uranium metal illustrating alterations found in colloids in dialyzed microdroplets of urines from patients affected with renal disease. *A*, numerous type O spherical colloids of varying sizes found associated with albuminuria. Twelve largest spheres are polystyrene latex particles. Types F and M colloids also present. *B*, clumped bacterial-like forms with associated 300 A.U. spheres found in urine from patient affected with toxemia of pregnancy. Nine polystyrene latex spheres are also near clumped bodies. *C*, jagged, pointed colloids found in urine from patients affected with urolithiasis with three polystyrene latex spheres. *D*, portion of microdroplet pattern of urine from patient affected with urolithiasis. Type O colloid appears to be spongelike and somewhat aggregated while great quantity of type M and type F colloid is also apparent. Two polystyrene latex spheres are also in picture.

terial was considered to be amorphous in character It had a moderate scattering power for the electron beam and was deposited as an overlying layer on other material It did not have any detectable thickness as interpreted by the metal-shadowing technique This type of material was assumed to be composed of noncrystallizing components that probably occur in the urine in the dissolved molecular form This amorphous material is also shown in figure 1, *C*

D) Colloids It was impossible to differentiate the colloids from the noncolloidal materials in the residues of the evaporated microdroplets of whole urine It was evident that dialysis was necessary before a study of the urinary colloids could be made

Studies of dialyzed preparations of these 30 normal urines failed to show any gross microdroplet patterns resembling those seen in the nondialyzed microdroplet residues Instead, isolated particles were usually found distributed in a random manner in the microdroplet areas

The most frequently occurring class of particles were spheroids approximately *100 A U in diameter These particles were found in all samples of normal urine* examined Their concentration was calculated to be approximately 10^{15} particles per ml of urine Occasionally these small particles appeared to be grouped into nearly amorphous structures This class of particles has been given the designation "Type M" (fig 2, *A*)

The most obvious particles in the dialyzed urines are spherical colloids varying in size from 300 A U to 800 A U Occasionally these appear to be smooth but more frequently they appear to have jagged surfaces In most of the specimens studied the concentration of these particles was calculated to be 10^{12} per ml of urine These particles were found in nearly every sample examined and have been designated as "Type O" Type O particles can be seen in figure 2, *A* and *C*

A third type of colloid is apparent in nearly all samples of urine examined These colloids are spherical particles 400 to 1000 A U in diameter that occur in three dimensional clusters Thousands of these may be clumped in one large connected mass with branches and side chains extending in all directions This colloid has been designated as "Type P" (fig 2, *B*)

A fourth type of colloid was apparent in nearly every sample of normal urine studied This was a filamentous form approximately 100 A U wide, 100 A U high, and 1500–6000 A U long Frequently these were found associated in netlike clumps that were circular in outline These filamentous forms are designated as "Type F" This colloid is considered to be identical with the urinary mucoprotein already described and photographed by Porter and Tamm[11] They studied this urinary colloid by direct vision with the electron microscope and considered that this component of the urine is derived from the walls of the bladder or urethra Since the dialyzing procedure used in these studies is even more gentle than the preparation procedures used by Porter and Tamm, it is believed that the circular clumps probably more nearly represent the naturally occurring state of this mucoprotein in the urine Type F colloids are shown in figures 2, *A* and 3, *D*

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[11] Porter, K R and Tamm I J Biol Chem **212** 135 1955

Occasionally (in about 10 per cent of the specimens studied) spindle-shaped colloids were found which were approximately 1300 A.U. long and 400 A.U. wide. The height appeared to be the same as the width. When these were found, their concentration was calculated to be approximately 10^{11} per ml. of urine. These spindle-shaped colloids were designated as "Type S" (fig. 2, *C*).

DISCUSSION

These electron microscope studies showed that more than 99 per cent of the solutes were removed from urine by dialysis. The particles remaining on the membrane after dialysis were considered to be the urinary colloids. However, in some instances part of the material left after a 72-hour dialysis appeared to be less readily soluble crystalloids of the urine.

Figure 2, *D* shows what we interpret to be crystals left on the membrane after the dialysis of the urine. It is apparent from the variations seen in the normal urines studied that the number, the amount, and the character (composition) of the urinary colloids will vary through a wide range which is probably dependent upon the total physiological activities of the organism. Since the urine studied was of the voided specimen, it not only represented the tubule fluid but also contained any products "picked up" in the passage of the urine down the collecting system. Alvarez[12] has shown in dogs that the normal vesical epithelium has a secretory activity.

The colloids of the urine occupy a unique place in renal physiology. Their origin, composition, and functions are poorly understood. The importance of the urinary colloids has centered around the question of their activity in stabilizing the solubility of the crystalloids[13] and in the maintenance of their own adequate dispersion.

If the crystalloids of the urine are dependent upon the protective action of the colloids for their solubility in the supersaturated liquid, then the colloids must be considered as a most important element of the urine. Much of the interest in the urinary colloids has thus centered about their importance as a possible factor in the prevention of, or the formation of, renal calculi.

It has been stated[5, 14, 15] that there is a crystalloid-colloid balance for the urine and that the solubility of the crystalloids is dependent on their adsorption by the colloids. A relative increase of the crystalloids (such as occurs in dehydration) may result in colloid conglomeration. This view has been questioned by Sisk and Toenhart.[16] They consider the factor most affecting the solubility of the insoluble salts to be the acidity of the urine and that the solvent action of the urine for uric acid must be attributed to the crystalloids of the urine and not the colloids. The protective action of the urinary colloids is further questioned by

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[16] Sisk, I. R. and Toenhart, Otto J.: J. Urol., **37:** 595, 1937.

Ferguson[17] and Newcomb.[18] Newcomb found that the original concentration of the urinary salts could be maintained after dialysis and evaporation provided that the acidity (pH) of the dialyzed portion is kept the same as the urine. Another component of the urine that increases the solubility of the other constituents of the urine is urea.

The composition of the urinary colloids was reported by Joly[14] as a mixture of chondroitin-sulphuric acid, glycogen, nucleic acid, mucin, and mucopolysaccharide. Electrophoretic studies of the urine by Boyce, Garvey and Norfleet[7] demonstrate in the urine all of the electrophoretic separable proteins present in normal plasma in addition to a mucoprotein and a complex polysaccharide. This could seem to indicate that glomerular filtration is a route by which some of the material arrives in the urine.

Pappenheimer,[19] as reported in Campbell's book,[9] in a study of the passage of substances across capillary walls, has estimated that the glomerular pores have a radius of 90 A U. Hall[20] has estimated the glomerular filtration pores at 100 A U in diameter. In a study of the anatomy of the glomerulus, Mueller et al.[21] "consider that filtration must occur through a thin layer of protoplasma," and Chinard[22] states that the glomerular capillary walls are jel-like structures rather than discrete holes of relatively uniform radius. The smallest material encountered in this study of the urine was a small spherical particle approximately 100 A U in diameter. Judged on the basis of the estimated size of the glomerular pores this colloid (Type M) might be the result of glomerular filtration. It is generally agreed that the normal urine contains small amounts of protein of glomerular origin. Regan and Heller[23] have shown by electrophoretic analysis several protein components in normal urine, the source of which is not clear.

The larger colloids might originate by the polymerization of smaller units within the urinary system, or they might come from disintegrating epithelial cells within the tubules. It is also possible that some of the urinary colloids may be secreted by the cells of the proximal convoluted tubules. However, experimental endeavors seem to suggest that the renal tubules do not excrete protein but, in fact, tend to absorb it.[20, 23] Rhodin,[24] in a study of the proximal convoluted tubule cells of the mouse kidney, observed granules between their brush borders and in the tubule lumen but drew no definite conclusion as to whether these granules were being absorbed or excreted.

Since in renal disease (nephritis) large amounts of protein are found in the urine and in renal calculus disease there is an increased output of urine, it seemed of interest to make comparative studies of normal and abnormal urines.

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[17] Ferguson, C J J Urol , 40· 672, 1938

[18] Newcomb, C Ind Med Research, 18 275, 1930

[19] Pappenheimer, J R New York Trans Third Conference Josiah Macy, Jr Foundation, 1952 chapt 1, Renal Function

[20] Hall, B V and Roth, L E Program of Electron Microscope Society of America, Nov 5, 1953

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[22] Chinard, F P New York Trans Third Conference Josiah Macy, Jr Foundation, 1952

[23] Regan D A and Heller, C G J

[24] Rhodin, Johannes Correlation of and Function in Normal and Experimentally Changed Cells of the Mouse Kidney Stockholm, 1954

All of the colloids found in the normal urines appear to be present in urines from patients affected with renal disease.

In a preliminary study of the urines from 6 patients with albuminuria, colloids of all types were found. In general these abnormal urines were characterized by increased amounts of spherical colloids (Type O) which appeared to vary continuously in size from 100 A.U. to 1300 A.U. These spherical colloids appeared to be at least 10 times as numerous as in the normal specimens studied. Figure 3, *A* is illustrative of the colloidal residues of albuminous urine.

Urine from one patient with toxemia of pregnancy was particularly interesting. Urine samples taken during the thirty-first week of pregnancy, when the urine albumin level was 700 mg. per 100 ml., were studied. This urine failed to yield any bacteria when subjected to the usual laboratory culturing tests. The electron microscope revealed not only the normal colloidal constituents but also clumps of bacterial-like forms averaging 1 to 1.5 microns in length by .5 microns in width. These clumped bodies were surrounded by numerous smaller spherical particles averaging 300 A.U. in diameter. These clumped bacterial-like forms were found in varying stages of disintegration, revealing smaller spherical particles within.

These spherical particles within the bacterial-like forms were the same size and shape as the numerous particles lying outside the forms (fig. 3, *B*). These pictures resemble many electron microscope pictures of known phage-infected bacteria. The occurrence of these clumped bacterial-like forms in this urine specimen was too numerous to be dismissed without speculation. The electron microscope evidence strongly suggests that a phage-infected bacterial infection was involved in the toxemia. Electron microscope studies of urine from the same patient one month after delivery failed to show any of the bacterial-like bodies with these associated 300 A.U. spheres, while the albumin level had likewise receded to normal.

Preliminary electron microscope studies were also made on urines from 5 patients affected with urolithiasis. As with the urines from patients affected with albuminuria, there appeared to be many more nondialyzable particles in these urines than in normal urines. These particles also differed somewhat in appearance from the particles in normal urines. The urine from the patients affected with calculi had numerous particles 400 to 1300 A.U. in diameter with irregular outlines. Agglutinated masses of larger, irregular particles were also present. These agglutinized particles had a unit length of 1200 to 2500 A.U.

The electron microscope evidence suggests that the Type O colloid is also modified in cases of urolithiasis. The typical Type O colloid was not usually seen; instead, similarly sized colloids possessing sharp points or projections such as those illustrated in figure 3, *C* were found. In some cases these colloids appeared to be somewhat sponge-like, such as those shown in figure 3, *D*.

The urine from one patient affected with uric acid stones was sampled immediately before and one hour after an injection of 300 turbidity reducing units of hyaluronidase. There was no noticeable change either in the form or number of nondialyzable colloids which might be attributed to this treatment.

Although only limited studies have been made on urines from patients affected with renal diseases, the evidence obtained indicates that an alteration in the number and form of the urinary colloids occurs. These studies have demonstrated that colloids are present in normal and abnormal urines, occurring in great numbers and existing in a variety of sizes and shapes.

SUMMARY

A spray droplet preparation method for the electron microscope study of nondialyzed evaporated urine residues is described which permits the differentiation of three general types of components. A polystyrene latex suspension was mixed with the urines studied to facilitate the calculation of the concentration and size of the urinary colloids. A dialyzing technique is presented which utilized a thin collodion film as the dialyzing membrane with a 7 mm. thick 7 per cent agar block lying between the membrane and distilled water. Gradients of available water, that are set up within the agar block, control the dialysis rate permitting a dialysis of the urine microdroplet residues without redistributing the colloids in the microdroplet patterns. Using this dialyzing technique, five distinctly different types of colloids were demonstrated to occur repeatedly as components of normal urine in specimens taken from 15 human males and 15 human females in the age group 20 to 30. One of these five types, Type F, is believed to be identical with a mucoprotein already described from urine. Changes in form and number of colloids were noted in urines from patients with renal disease. No change in colloid form or amount was apparent following hyaluronidase medication in one patient affected with uric acid calculi. Some theories concerning the possible origin of urinary colloids are discussed.

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THE PATHOGENESIS OF OSTEITIS PUBIS

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Within the past ten years there has been an increasing interest shown by urologists and radiologists in the condition known as osteitis pubis. This is a severely painful affliction of the pubis and adjacent musculature which in most cases has appeared at various intervals after suprapubic and retropubic prostatectomies. Cases have been reported following perineal and transurethral prostatectomies, cystotomy, ureterolithotomy, pyelitis, trauma, and abdominoperineal resection for carcinoma of the rectum. Several theories have been offered to explain the etiology of this disease, but many of the findings do not allow any single definite conclusion to be drawn, and all attempts to produce it in experimental animals have been unsuccessful.[1] Many excellent articles have been written reviewing in detail the historical and clinical aspects of osteitis pubis.[2, 3, 4] This paper is an attempt to explain the mechanisms by which osteitis pubis is produced using the technique of intraosseous phlebography.

In the usual case the patient first complains of mild pain over the pubis and stiffness of the thighs after a period of 10 days to 6 months from the performance of surgery or the occurrence of other inciting incidents. The pain and tenderness increase in severity and migrate to the ischial tuberosities. Extreme pain is produced by movement of the pelvic girdle or lower extremities and by bowel movement or by micturition. The attack is frequently accompanied by fever, increased sedimentation rate, leukocytosis, malaise, anorexia, and mental depression. In cases reported in the literature symptoms persist from 2 to 24 months and then subside.

When the condition is well developed, the roentgen appearance is diagnostic. Within two weeks of the onset of pain there may be a slight cortical erosion of the pubis adjacent to the symphysis or the inferior rami. Within the next week irregular, superficial destruction may extend to involve the main portions of the inferior rami and ischia. Occasionally the horizontal rami are included in the disease process. Following the cortical erosions a bilateral, symmetrical generalized demineralization of the pubic bones and ischia is seen. As a result of the cortical destruction the symphysis appears to widen. After various intervals there is evidence of bony repair. Subperiosteal new bone is formed, particularly

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in the regions of the symphysis and ischia Eventually the involved bones become thicker and more dense than normal, and there may be an obliteration of the symphysis produced by a fusion of the two pubic bones Four cases of associated arthritis of one or both hips have been reported [3]

ETIOLOGY

The many concepts advanced to explain the cause of osteitis pubis may be considered under the general headings of 1) trauma to the pubis, 2) infection, and 3) impaired circulation

Trauma Several investigators have suggested that injuries of the pubis due to the pressure of retractors, avulsion of rectus and transversalis fibers, and needle pricks were responsible [5] [10] In support of this supposition there have been five cases following external trauma to the pubis [11] However, Wheeler has failed to produce the lesion by pubic trauma and infection in rabbits,[12] and Beneventi and Spellman were unsuccessful in experiments on dogs after opening the bladder to allow seepage of urine, irritation of the obturator nerve, fulguration of the posterior pubis and excision of large wedges of fibrocartilage from the symphysis [1] Deliberate trauma to the pubic periosteum in cases of retropubic vesicourethral suspension operation of Marshall, Marchetti and Krants did not result in any observable damage to the pubic bone Also osteitis and osteomyelitis have been rare following pubiotomies and symphysiotomies [2]

Infection Infection is the most popular of the etiologies suggested for the condition The usual clinical course of mild fever, leukocytosis, development of sinus tracts, and increased sedimentation rate associated with the roentgen appearance of bone destruction and demineralization suggests that inflammation is present In fourteen cases in which biopsies of the pubis were obtained, thirteen showed some evidence of inflammation [3] [7] [8] [11] [13] [19] Cultures of the bone and exudate have revealed the presence of Pseudomonas aeruginosa, Bacillus proteus, and Bacillus coli [7] [15] [19]

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Against the theory that infection alone causes the disease are the unsuccessful attempts to produce the disease in experimental animals even with fulguration of the periosteum, irritation of the soft tissues, and free seepage of urine about the injured pubis.[1] The distribution of the lesion is entirely unlike that of osteomyelitis or osteitis in other parts of the body. One of the characteristic features of osteitis pubis is its almost symmetrical bilateral involvement of the pubis and ischia. It is hardly conceivable that an infectious process would remain limited to these areas and produce so uniform a picture. The usual lack of sequestration and the occurrence after trauma to the pubis also suggest that factors other than infection are responsible. Pseudomonas aeruginosa and Proteus vulgaris, organisms recovered from cultures of exudate and biopsy specimens, are frequent contaminants of surgical wounds and only rarely produce evidence of pathogenicity. A case of osteitis of the superior ramus of the pubis due to organisms of a similar type following perforation of the sigmoid colon has been encountered. Organisms cultured from a pelvic abscess adjacent to the pubis were Aerobacter aerogenes, Proteus vulgaris, Bacillus coli, Streptococcus faecalis, and Streptococcus viridans. Roentgenograms taken three months after the onset of symptoms revealed a diffuse sclerosis and thickening of bone (fig. 1). The distribution and roentgen appearance bear no resemblance to that found in osteitis pubis.

Impaired circulation. Adams and Chandler suggest the possibility that trauma to the pubis causes periosteal and subperiosteal damage resulting in thromboembolic occlusion of the end vessels. Beneventi mentions interruption of circulation as a theory but dismisses it from consideration with the observation that in the first 100 cases of cystectomy at the New York Hospital there was only one case of osteitis pubis. It is obvious that interference with the arterial circulation to bone would not produce the demineralization that is seen on roentgenograms since devitalized bone retains its normal mineral content. Batson has expressed the belief that trauma to the prostatic venous plexus and perhaps to the small vessel serving the pubis and ischia was a causative factor. The prostatic plexus drains the many small veins emerging from the posterior

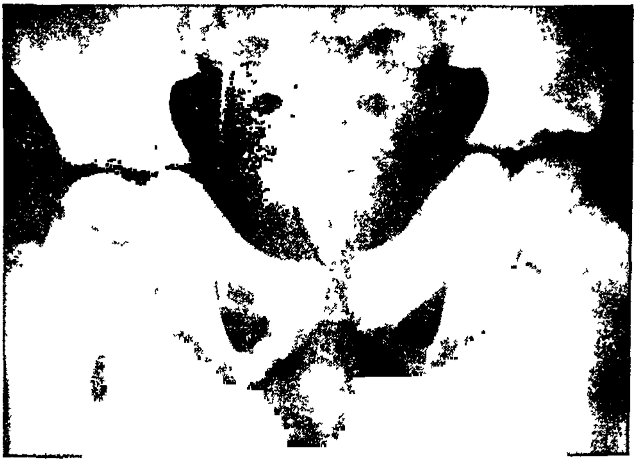

FIG. 1. Sclerosis and thickening of bone limited to lateral part of superior ramus of pubis secondary to pelvic abscess as result of perforation of sigmoid colon. Medial aspect of pubis is protected by capsule of symphysis pubis This does not resemble osteitis pubis.

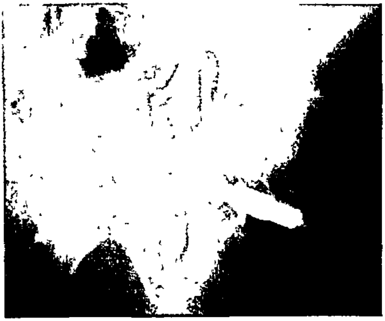

FIG. 2. Osseous phlebograms of left pubis. This film was obtained at completion of injection of 7 cc of 30 per cent urokon. Venous channels of bone drain rapidly into pudendal, vesical and prostatic plexuses. At this early stage, the pubic obturator, inferior gluteal and hypogastric veins are already filled. Some veins can be seen to drain toward left hip. Patient had no evidence of osteitis pubis.

aspect of the pubis and ischium. Damage to the prostatic plexus producing obstruction would cause dilatation of the veins and hyperemia which could result in demineralization of the bony structures.

Since the venous occlusion theory seemed to be the only one that would explain the roentgen features, it seemed worthwhile to see if venous occlusion was present. Therefore, attempts were made to demonstrate the venous drainage from the pubis in normal patients, after uncomplicated retropubic and suprapubic prostatectomies and in postoperative patients with osteitis pubis. To accomplish this, a technique was employed that has recently been used to demonstrate the venous drainage from various bones. This consists of the rapid injection of a water soluble contrast material into the venous sinusoids of the bone and the exposure of serial roentgenograms.[20, 21] Figure 2 demonstrates the venous drainage in a patient who had previously undergone suprapubic prostatectomy. The opaque material can be seen to be draining rapidly from the pubis through multiple small veins. These then drain into the pudendal, vesical, and prostatic venous plexuses and through the pubic veins to the obturator, inferior gluteal, and hypogastric veins. Where there is no venous obstruction the drainage is rapid; the larger pelvic vessels fill within two seconds after the completion of the injection. Osseous phlebography of the pubis was also performed on one patient who had a perineal prostatectomy and subsequent transurethral resection, three patients who had retropubic prostatectomies, and one woman who had an abdominoperineal resection for carcinoma of the rectum.

CASE REPORTS

Case 1. A patient who had typical symptoms and roentgenograms demonstrating osteitis pubis following a retropubic prostatectomy was studied. During the course of the injection, which was done under local anesthesia, there was an

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[20] Begg, A. C.: Intraosseous venography of lower limb and pelvis. Brit. J. Radiol., **27**: 318–324, 1954.

[21] Tori, Giulio: Radiological demonstration of azygos and other thoraco-abdominal veins in the living. Brit. J. Radiol., **27**: 16–22, 1954.

absence of pain. This was unusual in that all of the patients without osteitis pubis complained of mild to severe transient pain. The needle entered the softened bone very readily. The roentgenograms demonstrate huge dilated tortuous venous channels in the region of the osseous lesion on both sides of midline. Roentgenograms taken as long as 10 seconds later show no evidence of drainage to the main pelvic venous channels. Stereoscopically some of the vessels appear to be within the bone and others along the surface. A point of particular interest is the location of some of the dilated channels along the cortex of the inferior ramus of the pubis so that they fit within the cortical erosions seen on the plain films and typical of osteitis pubis. It appears certain that these vessels

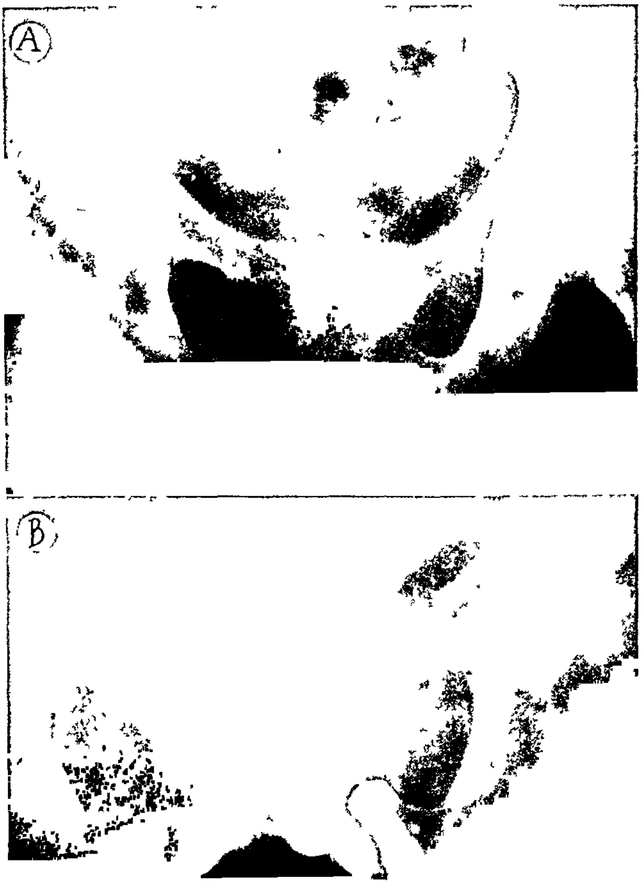

FIG. 3. *A*, osteitis pubis following retropubic prostatectomy. Roentgenograms were obtained 2 months after surgery and 1 month after onset of pain. There is a diffuse demineralization of medial aspect of superior ramus and entire inferior ramus of pubis. Some localized areas of erosion of cortex are present adjacent to symphysis and medial aspects of inferior rami.

B, osseous phlebogram of same patient. Roentgenogram obtained 10 seconds after completion of injection of 10 cc of 30 per cent urokon. Huge dilated, tortuous, venous channels are present with distribution almost identical to osseous lesion. No drainage to pelvic venous plexuses or deep pelvic veins Some of these vessels are within bone and others along its surface. Some dilated channels fit within cortical defects of inferior rami. A large vein appears to be causing erosion about symphysis pubis. Shadow at upper border of photograph is caused by barium in colon.

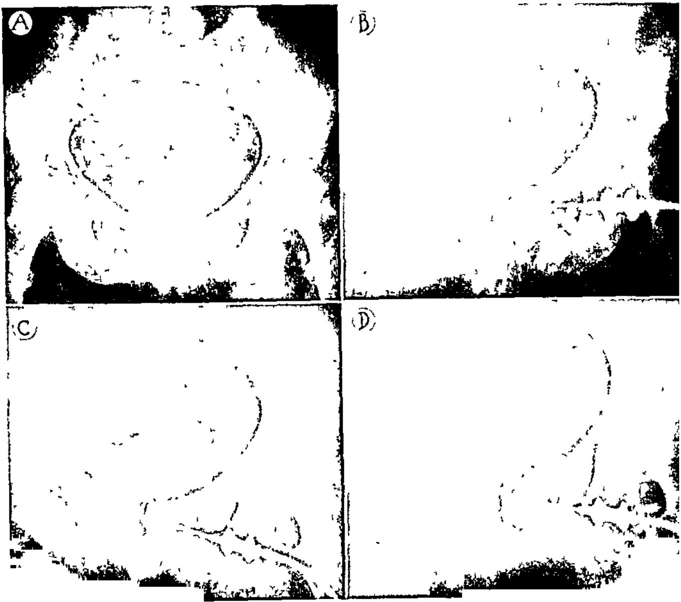

FIG. 4. *A*, probable osteitis pubis demonstrated about 4 months after an abdominoperi
resection for carcinoma of rectum. Onset of pain occurred about 2½ months after surg
Medial part of superior rami and inferior rami of pubis are demineralized. There is as
no significant degree of cortical erosion.

B, injection of 30 per cent urokon into superior ramus of pubis. Opaque material
entered many of the venous sinusoids of bone but there is very little drainage. Drain
that is present is through large vein extending toward hip region rather than through pe
veins.

C, second injection of 30 per c [illegible] edle inserted near s
physis pubis. Opaque material i [illegible] oids of bone and s
smaller veins along superior marg [illegible] left hip. A rather la
vein in the symphysis is filled Compare with figure 2 in which pelvic veins are rapidly fil

D, obtained about 6 seconds after *C*. Obturator and hypogastric veins are filled but th
is no significant degree of filling of pelvic venous plexuses. There is a considerable degre
delay in filling of vessels.

are interposed between the periosteum and cortical bone and have caused
erosion of the cortical surface. A large dilated vein can also be seen superimpo
upon the symphysis pubis. This vein fits into the space of the widened symph
and could have produced the apparent widening by the effect of pressure u
the adjacent cortical surfaces (fig. 3).

Case 2. A female patient with symptoms of severe pubic pain occurring
proximately 2½ months after abdominoperineal resection for carcinoma of
rectum and roentgenograms resembling osteitis pubis had an osseous phlebogr
approximately four months later. On the first injection into the superior ra
of the left pubis the opaque material remained within the bone (fig. 4).
needle was reinserted into the inferior margin of the body of the left pubis

the injection repeated. The contrast solution eventually passed into the larger pelvic veins but the rate of transit appeared slower than usual with the obturator vein not filling until approximately five seconds after the completion of the injection. Several small vessels can be seen along the cortical surface of the inferior ramus of the pubis and a large vein along the symphysis pubis.

DISCUSSION

It would appear that case 2 could represent the first phase of osteitis pubis in which there has been some interference with venous flow from the pubic bone to the pelvic veins. Some of the blood does pass from the inferior ramus to these vessels but the rate of its flow is diminished. This partial obstruction to flow has produced a venous stasis within the pubic bone. Such venous stasis could result in demineralization of the bone due to pressure by the vessels upon the bony trabeculae. Case 1 represents an advanced stage in which there is a complete obstruction of the venous drainage, in the presence of normal arterial supply, from the medial end of the pubis and ischium. There is no filling of the pelvic venous plexuses indicating that they are completely occluded. The position of the characteristic cortical defects usually seen along the symphysis and medial aspects of the inferior rami of the pubis suggests that they are due to erosion by the dilated venous channels situated between the cortex and periosteum. During the healing stage the periosteum, which has been stripped from the underlying bone and perhaps stimulated by the associated inflammatory reaction, lays down new bone much as it does in osteomyelitis and scurvy. This produces the widened sclerotic bones and fusion of the symphysis that are seen in "healed" lesions.

Two factors remain to be explained: 1) The cause of the venous obstruction remains to be demonstrated. This could be due to the surgical procedure and result from suture and fulguration of the vessels of the prostatic, vesical and pudendal venous plexuses or from thrombophlebitis as a result of trauma to the vessels. Thrombophlebitis may be the cause in the patients who have not undergone surgery. A combination of both may be involved. 2) The presence of microscopic evidence of inflammation and bacteriologic evidence of infection with avirulent organisms needs to be explained. It seems most likely that these organisms which are relatively resistant to most antibiotics used in modern urological surgery are secondary invaders. Ordinarily they would not be pathogenic, but in the presence of venous stasis and devitalized tissue they are capable of producing a low-grade inflammatory reaction. The mechanism by which roentgen therapy and cortisone have produced an alleviation of symptoms is probably due to a reduction of the inflammatory reaction. The means by which one or both hips may become involved, as reported in four cases in the literature, can be postulated on the same basis. As seen in the osseous phlebograms there is some drainage from the pubic bone to the vessels surrounding the hip and the femoral vein (fig. 2).

We wish to express our appreciation to Dr. Robert Raphael and Dr. Phillip Lahr for their help in conducting this investigation.

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A NO-COST DISPOSABLE URINARY DRAINAGE APPLIANCE

WILLIAM B BIRCH

For the last 6 months, at our hospital, we have been employing the used venopak and liter bottle as a satisfactory urinary drainage appliance (fig 1) There has been an unlimited supply of these used tubes and bottles which were formerly discarded

The apparatus is assembled in this manner The Murphy adapter is removed from its elastic mounting and the small metal drip extracted with a hemostat The air filter is removed and discarded The dispensing cap is then unscrewed and the small metal adapter in the inner air filter hole is likewise removed with a hemostat The pinch clamp on the plastic tubing and the distal gum tubing and its terminal plastic adapter are removed The metal ring is then removed from the liter bottle The tubing, glass adapter and bakelite cap are then cleaned under the tap and placed in a solution of mercury cyanide or aqueous zephiran The bottle is cleansed with tincture of green soap and rinsed clear under the tap to remove any traces of sugar or other ingredients which may remain

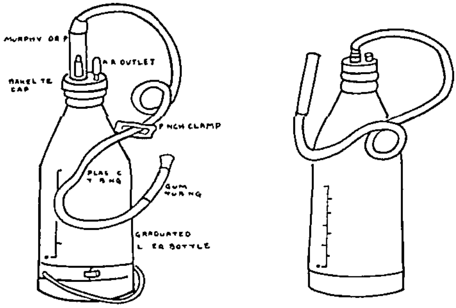

Fig 1

The appliance is assembled by replacing the bakelite cap on the bottle and inserting the distal plastic adapter into the hole which originally contained the small metal Murphy drip A small pledget of sterile cotton is inserted into the now distal glass adapter and the tubing wrapped around the bottle and placed in a paper carton The top is folded and clipped with metal fasteners This is performed in our central supply room and sufficient appliances are placed on the floors for ready use The photograph shows the apparatus before and after arrangement

After a retention catheter is in place and the physician desires constant drainage, the glass portion of the Murphy drip is then inserted into the catheter and the bottle placed on a small stool beside the bed The tubing is practically kinkproof and is of sufficient length to accommodate change of position of the patient in bed

Accepted for publication June 21, 1955

These appliances were subjected to a 3-month trial on the urological service before recommending them for the entire hospital. No objections whatsoever have been encountered. They have been used on the first postoperative day following transurethral and suprapubic prostatectomies where the drainage was many times quite bloody. Patients stated that the appliances were less confining to their movements, drained better and were less noticeable than rubber tubing. For the last 6 months, they have been used on all services where urinary drainage was desired and also several cases of common duct drainage following surgery. No objections have been encountered. An unlimited supply exists and the entire appliance can be discarded and a new one employed every two or three days. The graduated liter bottle serves as an excellent measure for output records.

CONCLUSION

A no-cost disposable urinary drainage appliance has been adequately tested and recommended for use. Aside from complete satisfaction of this appliance, there exists a marked saving to the hospital from expensive rubber tubing and glass adapters.

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North Central—Cleveland, Ohio, October 3 5 1956
South Central—Mexico City, dates to be announced later
Southeastern—Hollywood Beach, Fla March 25-29 1956
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